I5Q-MC-CGAI (a) Clinical Protocol

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of LY2951742 in Patients with Chronic Migraine – the REGAIN Study

NCT02614261

Approval Date: 22-Jan-2016

Protocol I5Q-MC-CGAI(a)
A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of LY2951742 in Patients with Chronic Migraine – the REGAIN Study

Confidential Information

LY2951742

Study CGAI is a Phase 3, multisite, double-blind, randomized, placebo-controlled, 3-month study to compare the efficacy and safety of two doses of LY2951742 in preventing migraine headaches in patients suffering from chronic migraine. Patients may continue into a 9-month open-label extension following the double-blind treatment period.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol Electronically Signed and Approved by Lilly: 23 September 2015
Protocol Amendment (a) Electronically Signed and Approved by Lilly on approval date provided below

Approval Date: 22-Jan-2016 GMT

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1. Protocol Synopsis

Title of Study:
A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of LY2951742 in Patients with Chronic Migraine – the REGAIN Study.

Rationale:
Study 15Q-MC-CGAI (CGAI; REGAIN) will enable a comprehensive clinical assessment of two doses of LY2951742 in a patient population for which the medical need is substantial. This study, along with 2 studies in patients with episodic migraine, is part of a Phase 3 clinical program that is intended to provide pivotal efficacy data to support a registration in patients with migraine.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary To test the hypothesis that at least 1 dose of LY2951742 (120 mg or 240 mg/month) is superior to placebo in the prevention of migraine headache in patients with chronic migraine	The overall mean change from baseline in the number of monthly migraine headache days during the 3-month double-blind treatment phase
Key Secondary Objectives If LY2951742 (120 or 240 mg/month) is statistically significantly superior to placebo on the primary objective, the following key secondary objectives will be tested with adjustment for multiplicity (only the key secondary objectives are listed below):	The specific methodology (including testing order, relationship and type I error allocation and propagation) for the tests of the following key secondary endpoints will be specified in the statistical analysis plan:
• To compare LY2951742 with placebo with respect to 50% response rate	• The proportion of patients with reduction from baseline ≥50% in monthly migraine headache days during the 3-month double-blind treatment phase
• To compare LY2951742 with placebo with respect to 75% response rate	• The proportion of patients with reduction from baseline ≥75% in monthly migraine headache days during the 3-month double-blind treatment phase
• To compare LY2951742 with placebo with respect to 100% response rate	• The proportion of patients with reduction from baseline of 100% in monthly migraine headache days during the 3-month double-blind treatment phase
• To compare LY2951742 with placebo with respect to change in functioning	• Mean change from baseline in the Role Function-Restrictive domain score of the Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1) at Month 3

Objective(s)/Endpoints:

Objectives	Endpoints
• To compare LY2951742 with placebo with respect to change in use of acute (abortive) migraine treatment	• The overall mean change in the number of monthly migraine headache days requiring medication for the acute treatment of migraine or headache during the 3-month double-blind treatment phase
• To compare LY2951742 with placebo with respect to change in global severity of the migraine condition	• The mean change from baseline in the Patient Global Impression of Severity (PGI-S) score at Month 3

Summary of Study Design:

A multisite, randomized, double-blind, parallel, placebo-controlled trial with 5 study periods in patients who meet International Classification of Headache Disorders (ICHD) criteria for a diagnosis of chronic migraine as confirmed during a prospective baseline period.

Treatment Arms and Duration:

Three treatment arms: LY2951742 (120 mg/month [administered as 1 injection] with a 240 mg loading dose), LY2951742 (240 mg/month, administered as 2 injections of 120 mg), and placebo. Following a prospective baseline period (30 to 40 days), eligible patients will be randomized in a 2:1:1 ratio to receive placebo, 120 mg/month of LY2951742, or 240 mg/month of LY2951742, respectively, and will begin a 3-month double-blind treatment phase. Patients who complete the double-blind period may enter a 9-month open-label extension phase for treatment with LY2951742. All patients entering the open-label period will receive an initial dose of 240 mg of LY2951742 at the first open-label visit. At the second open-label visit, all patients will receive a 120 mg dose of LY2951742; dosing at subsequent visits will be flexible (either 120 mg or 240 mg/month) at the discretion of the investigator. All patients will also be followed for a 4-month, post-treatment phase during which patients will no longer receive any study medication.

Number of Patients:

The study will screen an estimated 1833 potential study participants to ensure randomization of a minimum of 825 patients with chronic migraine. The study will include a potential sample size re-estimation to increase the final sample size at an interim analysis, if indicated, to maintain a well-powered study.

Statistical Analysis:

Unless otherwise specified, analyses will be conducted on an intent-to-treat (ITT) population, which includes all patients who are randomized and receive at least one dose of investigational product. Patients in the ITT population will be analyzed according to the treatment group to which they are randomized. When change from baseline is assessed, the patient will be included in the analysis only if he/she has a baseline and a postbaseline measurement.

The primary analysis will evaluate the efficacy of two doses of LY2951742 compared with placebo on the overall mean change from baseline in the number of monthly migraine headache days during the 3-month double-blind

treatment phase. Migraine headache day will be defined to include both migraine and probable migraine days. The primary analysis will be performed using a restricted maximum likelihood-based mixed models repeated measures technique. The analysis will include the fixed categorical effects of treatment, baseline medication overuse (yes/no), use of concurrent migraine prophylaxis (yes/no), pooled country, visit, and treatment-by-visit interaction, as well as the continuous fixed covariates of baseline number of migraine headache days and baseline number of migraine headache days-by-visit interaction.

2. Introduction

2.1. Background

Migraine is a chronic, debilitating condition found to be one of the top 10 causes of disability expressed as years lived with disability globally (Vos et al. 2012). Buse and colleagues report that chronic migraine sufferers experience substantially greater disease burden than those with episodic migraine, including greater rates of headache-related disability, quality of life, comorbid medical and psychiatric conditions, and health care resource utilization (Buse et al. 2012). However, one study estimates that only a small fraction of patients receive preventive treatment, although more than 25% of migraineurs are in need of preventive therapy (Rizzoli 2014). Despite the availability of preventive medications for migraine, significant needs remain for new treatment options with improved efficacy and tolerability.

Chronic migraine is defined by the International Headache Society (IHS) International Classification of Headache Disorders (ICHD)-3 beta guidelines (1.3) as headache occurring on 15 or more days per month for more than 3 months; the headache must have the features of migraine headache on at least 8 days per month (ICHD-3 2013). Although chronic migraine is less prevalent than episodic migraine, its sufferers experience frequent headaches and a high degree of disability (Bigal et al. 2013).

Calcitonin gene-related peptide (CGRP), a 37-amino acid neuropeptide, is widely expressed throughout the central and peripheral nervous system and acts as a local facilitator of inflammatory processes. Calcitonin gene-related peptide is implicated in the pathophysiology of migraine and is hypothesized to be involved in the release of inflammatory mediators and the transmission of nociceptive (pain) information from intracranial blood vessels to the nervous system (Villalón and Olesen 2009). In migraineurs, serum concentrations of CGRP are significantly elevated during migraine attacks (Goadsby et al. 1990; Goadsby and Edvinsson 1993), and infusion of CGRP to individuals with a history of migraine can trigger migraine attacks (Lassen et al. 1998; Lassen et al. 2002). The neutralization of CGRP with antibodies has been shown to modulate neurogenic inflammation; thus, these antibodies may represent a promising pharmacologic approach for the prevention of migraine (Investigator's Brochure [IB], Section 3.1).

LY2951742 is a humanized monoclonal antibody that potently and selectively binds to CGRP, preventing CGRP-mediated biological effects (IB, Section 3.1). To date, more than 450 clinical trial participants have been exposed to LY2951742 at single doses ranging from 1 to 600 mg and multiple doses up to 300 mg in 5 clinical trials of LY2951742. In studies of patients with migraine (Studies I5Q-MC-ART1 [ART-01] and I5Q-MC-CGAB [CGAB]), efficacy data have demonstrated that LY2951742 had significantly greater mean reductions than placebo in migraine headache days and other efficacy parameters. Across clinical studies of LY2951742, assessment of adverse events (AEs) indicates that LY2951742 has been well tolerated in both healthy subjects and in patients with episodic migraine. The AEs generally have been mild to moderate in severity. In two studies of patients with migraine, the most frequently reported adverse events (AEs) included injection-site pain, upper respiratory tract infection, abdominal

pain, dizziness, injection-site erythema, rash, hypertension, and nasopharyngitis. Analyses of laboratory values and cardiovascular monitoring of the clinical studies have shown no other clinically important changes in tested parameters.

2.2. Study Rationale

Study I5Q-MC-CGAI (REGAIN) will enable a comprehensive clinical assessment of LY2951742 in a patient population for which the medical need is substantial. This study, along with 2 studies in patients with episodic migraine, is part of a Phase 3 clinical program that is intended to provide pivotal efficacy data to support a registration of LY2951742 for patients with migraines. REGAIN will include up to 12 months on investigational product (3 months of double-blind treatment and 9 months of open-label treatment) followed by 4 months of post-treatment observation to deepen understanding of the effects of a CGRP antibody in preventing chronic migraines.

3. Objectives and Endpoints

Table CGAI.1 shows the key objectives and endpoints of the study. Table CGAI.2 provides definitions for the terms referenced below.

Table CGAI.1. Objectives and Endpoints

Objectives	Endpoints
Primary To test the hypothesis that at least 1 dose of LY2951742 (120 or 240 mg/month) is superior to placebo in the prevention of migraine headache in patients with chronic migraine.	The overall mean change from baseline in the number of monthly migraine headache days during the 3-month double-blind treatment phase.
Key Secondary Objectives If LY2951742 (120 or 240 mg/month) is statistically significantly superior to placebo on the primary objective, the following key secondary objectives will be tested with adjustment for multiplicity:	The specific methodology (including testing order, relationship and type I error allocation and propagation) for the tests of the following key secondary endpoints will be specified in the statistical analysis plan:
• To compare LY2951742 with placebo with respect to 50% response rate	• The proportion of patients with reduction from baseline ≥50% in monthly migraine headache days during the 3-month double-blind treatment phase
• To compare LY2951742 with placebo with respect to 75% response rate	• The proportion of patients with reduction from baseline ≥75% in monthly migraine headache days during the 3-month double-blind treatment phase
• To compare LY2951742 with placebo with respect to 100% response rate	• The proportion of patients with reduction from baseline of 100% in monthly migraine headache days during the 3-month double-blind treatment phase
• To compare LY2951742 with placebo with respect to change in functioning	• The mean change from baseline in the Role Function-Restrictive domain score of the Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1) at Month 3
• To compare LY2951742 with placebo with respect to change in use of acute (abortive) migraine treatment	• The overall mean change in the number of monthly migraine headache days requiring medication for the acute treatment of migraine or headache during the 3-month double-blind treatment phase
• To compare LY2951742 with placebo with respect to change in global severity of the migraine condition	• Mean change from baseline in the Patient Global Impression of Severity (PGI-S) score at Month 3

Table CGAI.1. Objectives and Endpoints (continued)

Objectives (cont.)	Endpoints (cont.)
Other Secondary Objectives	
• To compare LY2951742 with placebo with respect to change in headache days	• The overall mean change from baseline in the number of monthly headache days during the 3-month double-blind treatment phase
• To compare LY2951742 with placebo with respect to change in moderate to severe headache days	• The overall mean change from baseline in the number of monthly moderate to severe headache days during the 3-month double-blind treatment phase
• To compare LY2951742 with placebo with respect to 30% response rates	• The proportions of patients demonstrating ≥30% reduction from baseline in the number of monthly migraine headache days during the 3-month double-blind treatment phase
• To compare LY2951742 with placebo with respect to distribution of response rates	• Cumulative distribution of monthly migraine headache day response rates during the 3-month double-blind treatment phase
• To compare LY2951742 with placebo with respect to time to 50% response	• Time to first occurrence of a ≥50% reduction from baseline in the number of monthly migraine headache days (Kaplan-Meier analysis)
• To compare LY2951742 with placebo with respect to onset of effect	• The initial month at which statistical separation in mean change from baseline in the number of monthly migraine headache days is demonstrated and maintained through Month 3
• To compare LY2951742 with placebo with respect to onset of 50% sustained response	• The initial month at which statistical separation in the proportion of patients meeting at least a 50% reduction in monthly migraine headache days that is maintained at all subsequent months through Month 3
• To compare LY2951742 with placebo with respect to maintenance of 50% response	• The proportion of patients who maintain 50% response criteria for all 3 months of double-blind treatment
• To compare LY2951742 with placebo with respect to changes in other efficacy parameters, specifically: o International Classification of Headache Disorders (ICHD) migraine headache days o migraine attacks o migraine headache hours o headache hours o severity of remaining migraines	• The overall mean change from baseline (during the 3-month double-blind treatment phase) on the following monthly measures: o International Classification of Headache Disorders (ICHD) migraine headache days o migraine attacks o migraine headache hours o headache hours o severity of remaining migraines
• To compare LY2951742 with placebo with respect to global assessment of illness	• Overall mean Patient Global Impression-Improvement (PGI-I) rating during the 3-month double-blind treatment phase

Table CGAI.1. Objectives and Endpoints (continued)

Objectives (cont.)	Endpoints (cont.)
Other Secondary Objectives (cont.)	
• To compare LY2951742 with placebo with respect to changes in disability and quality of life	• Changes from baseline to Month 3 on the following measures: o Migraine Disability Assessment test (MIDAS) total score and individual items o MSQ v2.1 total score, and Role Function-Preventive and Emotional Function domain scores o Health Care Resource Utilization and Employment Status
• To compare LY2951742 with placebo with respect to safety and tolerability	• Analysis of: o treatment-emergent adverse events (TEAEs) o discontinuation rates o vital signs and weight o electrocardiograms (ECGs) o laboratory measures o other safety parameters, including suicidality using the Columbia-Suicide Severity Rating Scale (C-SSRS)
• To evaluate LY2951742 with respect to immunogenicity	• Throughout the study: o Development and consequences of anti-drug antibodies and neutralizing anti-drug antibodies to LY2951742
• To evaluate LY2951742 with respect to pharmacokinetics	• Serum concentrations of LY2951742
• To evaluate LY2951742 with respect to pharmacodynamics (target engagement)	• Plasma concentrations of CGRP
• To assess changes in efficacy, safety, and functional outcomes during Study Period IV (open-label treatment)	• In Study Period IV: o Mean changes in all continuous measures of efficacy, safety, and functional outcomes that are also assessed in the double-blind period o Among patients previously treated with LY2951742 who met 50% response criteria at Month 3 in the double-blind treatment period, the proportion of patients who demonstrate response for at least 6 of the 9 months in the open-label treatment period

Table CGAI.1. Objectives and Endpoints (continued)

Objectives (cont.)	Endpoints (cont.)
Other Secondary Objectives (cont.) • To assess changes in efficacy outcomes during Study Period V as collected by electronic patient-reported outcomes (ePRO) diary data	• In Study Period V: ○ Changes in the number of monthly migraine and headache days from the baseline to the end of the post-treatment follow-up phase ○ Time to first loss of response among patients who met 50% response criteria at their last injection interval ○ Time to initiation of treatment with a migraine prevention medication
Tertiary Objectives	
CCI	
• To explore the effect of LY2951742 on non-migraine chronic pain	• Mean change from baseline in average pain severity of other chronic pain conditions
• To compare LY2951742 with placebo with respect to categorical changes in quality of life	• Percentages of patients with: ○ ≥50% improvement in MIDAS total score ○ change from baseline in MSQ Role Function-Restrictive domain ≥10.9 ○ change from baseline in MSQ Role Function-Preventive domain ≥8.3 ○ change from baseline in MSQ Emotional Function domain ≥12.2
• To compare LY2951742 with placebo with respect to the proportion of migraine headache days requiring medication for the acute treatment of migraine or headache	• Change from baseline in the proportion of monthly migraine headache days requiring medication for the acute treatment of migraine or headache
• To compare LY2951742 with placebo with respect to changes in symptomatology associated with migraine or probable migraine	• Change from baseline in the number of monthly migraine headache days with: ○ nausea and/or vomiting ○ photophobia and phonophobia ○ aura ○ prodromal symptoms other than aura

Table CGAI.2. Migraine and Headache Endpoint Definitions

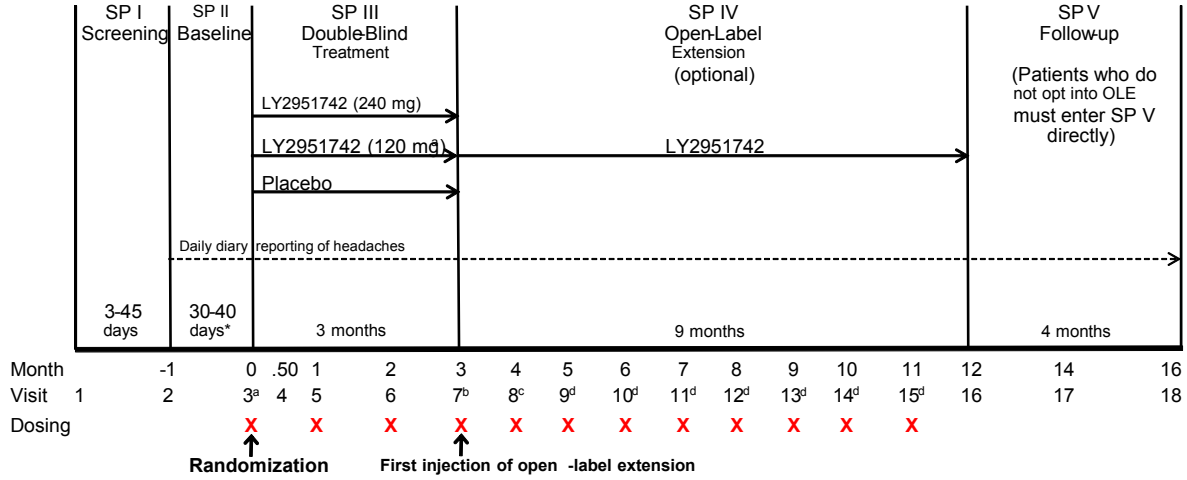
Diagnosis	Definition/Criteria
Migraine headache	A headache, with or without aura, of ≥30 minutes duration which meets criteria A and B or meets criterion C: A. At least 2 of the following headache characteristics: • Unilateral location • Pulsatile quality • Moderate or severe pain intensity • Aggravation by or causing avoidance of routine physical activity AND B. During headache at least one of the following: • Nausea and/or vomiting • Photophobia and phonophobia OR C. The headache is believed by the patient to be migraine at onset and is relieved by a triptan or ergot derivative *(Definition adapted from the Standard International Headache Society [IHS] International Classification of Headache Disorders (ICHD)-3 beta)*
Probable migraine	A headache missing 1 of the migraine features in the IHS ICHD-3 beta definition such that one feature in criteria A is missing or one feature in criteria B is missing; that is, meet at least 2 A criteria and none of the B criteria or meet 1 of the A criteria and at least 1 of the B criteria. It must not meet criterion C.
Migraine headache day (primary objective)	A calendar day on which a migraine headache or probable migraine headache occurred.
Migraine headache attack	Beginning on any day a migraine or probable migraine headache is recorded and ends when a migraine-free day occurs.
Non-migraine headache	All headaches of at least 30 minutes duration not fulfilling the definition of migraine or probable migraine are classified as non-migraine headaches.
Non-migraine headache day	A calendar day on which a non-migraine headache occurred.
Headache day	A calendar day on which any type of headache occurs (including migraine headache, probable migraine headache, and non-migraine headache).

4. Study Design

4.1. Overview of Study Design

Study CGAI (REGAIN) is a Phase 3, multisite, double-blind, randomized, placebo-controlled, study of LY2951742 in patients suffering from chronic migraine. The study has 5 periods, including a prospective baseline phase to determine patient eligibility.

Figure CGAI.1 illustrates the study design.



*Eligibility period determined between a minimum of 30 days and a maximum of 40 days. Investigators may have up to 5 additional days (beyond the 40 days) if needed to schedule patients' Visit 3 appointment.

[a] Patients randomized to the 120 mg dose will receive a loading dose of 240 mg at the first injection only (Visit 3).
[b] At Visit 7, all patients who enter the open-label extension will receive LY2951742 at a dose of 240 mg.
[c] At Visit 8, all patients will receive LY2951742 at a dose of 120 mg.
[d] Starting at Visit 9, dosing will be flexible (LY2951742 120 mg or 240 mg) at the discretion of the investigator.

Abbreviations: OLE = open-label extension; SP = study period.

Figure CGAI.1. Illustration of study design for Clinical Protocol I5Q-MC-CGAI.

Study Period I: The study and potential risks will be explained to the patient at Visit 1. The informed consent form (ICF) must be signed before any study procedures are performed. Patients are required to discontinue all excluded medications or treatments for migraine prevention at least 30 days prior to Visit 2. Botulinum toxin A or B in the head or neck area must be discontinued at least 4 months prior to Visit 2.

The screening visit (Visit 1) will consist of a full clinical assessment, including a comprehensive medical evaluation documenting medical history, and a physical and neurological examination (Appendix 2). Visit 1 will be complete when the last scheduled procedure of the screening assessment for the patient is completed.

Study Period II: Qualified patients will enter Study Period II (prospective baseline) to determine their eligibility for the study and to establish baseline data for comparison of endpoints during the double-blind treatment period. Beginning at Visit 2, patients will log in daily to the

electronic patient-reported outcomes (ePRO) system to answer questions about the occurrence of headaches, headache duration, headache features, severity of headache, and use of headache medication. At the end of the prospective baseline period, sites will be notified whether their patients met criteria and are eligible to be randomized at Visit 3.

To avoid biased reporting, patients must not be told the number of headache days or migraine headache days on which study qualification is based.

Study Period III: At the start of the 3-month double-blind treatment phase (Visit 3), patients meeting all eligibility requirements will be randomized to 1 of 3 treatment groups in a 2:1:1 ratio to receive placebo, 120 mg/month LY2951742, or 240 mg/month LY2951742, respectively. At Visit 3, if available and where local regulations and Ethical Review Boards allow, patients will also watch a training video designed to address patient expectations with regard to participation in a placebo-controlled trial and the difference between medical treatment and research. To preserve blinding throughout the study, patients in all treatment groups will receive 2 injections of investigational product at each dosing visit (two placebo injections, two 120-mg LY2951742 injections, or one placebo injection and one 120-mg injection). Patients randomised to the 120-mg dose of LY2951742 will receive an initial loading dose of 240 mg (2 injections of 120 mg each).

The patient will be considered enrolled in the study when randomization occurs. During this phase, study procedures at dosing visits must always occur prior to the patient receiving their assigned treatment.

Patients will be given investigational product (LY2951742 or placebo) injections during office visits (Figure CGAI.1). For all treatment groups, investigational product is administered by subcutaneous injection once monthly at the dosing visits. At Visit 3 (first dose), patients are required to remain in the office for observation for 30 minutes post injection. Patients will continue to log in and complete the ePRO diary each day. Patients may continue to take their allowed acute migraine headache medication (with some limitations; see Section 6.8) during the treatment phase.

Patients will receive their last double-blind dose of investigational product at Visit 6. Patients who do not opt to continue into Study Period IV will receive no further injections and will proceed directly to the post-treatment follow-up phase.

Study Period IV: Patients who complete the double-blind treatment phase (Study Period III) can opt to enter an open-label treatment period (Study Period IV) for up to 9 months of treatment with LY2951742. Sites and patients will remain blinded to patients' previous treatment assignments. All patients entering the open-label period will receive an initial dose of 240 mg of LY2951742 at Visit 7 and will remain at the office for a 30-minute post-injection observation at this visit. Injections after Visit 7 will not require an observation period. At Visit 8, all patients will receive a 120 mg dose of LY2951742; dosing at subsequent visits (beginning at Visit 9) will be flexible (either 120 mg or 240 mg/month) at the discretion of the investigator. Dosing and dose changes can only occur at regular visits (once monthly). Patients will continue to have efficacy and safety assessed, including daily completion of the ePRO diary (see Appendix 2,

Schedule of Activities). Patients may continue to take their allowed acute migraine headache medication as in Study Period III.

Study Period V: Patients who discontinue from Study Period III or IV must enter directly into Study Period V for assessment during washout of investigational study drug. During this 4-month phase, sites and patients will continue to remain blinded to patients' original double-blind treatment assignments. Patients will follow all study procedures during Study Period V but will not receive investigational product. One month after Visit 16, if clinically warranted due to a worsening of symptoms, patients may start migraine prevention medication(s) at the discretion of the investigator (Section 6.6.1). The list of allowed preventive medications is provided in Section 6.8. At Visit 18 (Month 16), patients will return to the site for their last study visit and discharge from the study.

4.2. End of Trial Definition

End of the trial is the date of the last visit or last scheduled procedure shown in the Schedule of Activities (Appendix 2) for the last patient.

4.3. Scientific Rationale for Study Design

The length of the randomized, double-blind treatment phase (3 months) is considered a sufficient duration to assess the safety and efficacy of a migraine prevention medication given the mechanism and observed onset of action for CGRP antibodies (Dodick et al. 2014a, 2014b). Furthermore, a placebo-controlled study with a duration longer than 3 months may not be tolerated by patients suffering from chronic migraine. A 4-month post-treatment follow-up phase is included to evaluate patient safety during wash-out of LY2951742. This allows for a total of 5 months of observation from the time of last injection of LY2951742. A 5 -month post-treatment observation period allows for a wash-out of approximately 5 elimination half-lives of LY2951742 and should decrease LY2951742 serum concentrations by approximately 97% during this time.

4.4. Justification for Dose

Doses of 120 mg and 240 mg administered once monthly were selected primarily on the basis of clinical efficacy and pharmacokinetic/pharmacodynamic data from the Phase 2 dose-ranging study. Results from the dose-ranging study indicate that 120 mg was statistically significantly superior to placebo at the last 28-day period of the 3-month treatment phase in mean change in migraine headache days, as well as other measures of efficacy and quality of life. The use of a loading dose for the 120 mg treatment arm, and the inclusion of a 240 mg treatment arm, is based on the finding that a dose higher than 120 mg achieved statistically significant separation from placebo as early as Month 1. The doses of 120 mg and 240 mg LY2951742 planned for Study CGAI also are being evaluated in two other pivotal efficacy studies of LY2951742 (both in patients with episodic migraine).

4.5. Benefit/Risk Assessment

More information about the known and expected benefits, risks, serious adverse events (SAEs) and reasonably anticipated adverse events (AEs) of LY2951742 are to be found in the Investigator's Brochure (IB).

5. Study Population

All patients must meet the following selection criteria. Eligibility of patients for study enrollment will be based on the results of a screening medical history, physical examination, neurological examination, clinical laboratory tests, electrocardiograms (ECGs), and migraine history during screening and the prospective baseline period, as described in the Inclusion and Exclusion Criteria sections. The nature of any comorbid conditions present at the time of the physical examination and any preexisting conditions must be documented. Individuals who do not meet the criteria for participation in this study (screen failure) for specific reasons as outlined may be considered for re-screening once, with approval from Eli Lilly and Company (Lilly) Medical (Section 5.3).

Study participants should be instructed not to donate blood or blood products during the study or for 5 months following the last administration of investigational product.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

5.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet all of the following criteria at screening:

Patient and Disease Characteristics

[1] Patients are 18 to 65 years of age (inclusive) at the time of screening.

[2] Have a diagnosis of chronic migraine as defined by the IHS ICHD-3 beta guidelines (1.3) (ICHD-3 2013), that is, a headache occurring on 15 or more days per month for more than 3 months, which has the features of migraine headache on at least 8 days per month.

[3] Migraine onset prior to age 50.

[4] Prior to Visit 1, a history of at least 1 headache-free day per month for the past 3 months.

[5] From Visit 2 to Visit 3 (prospective baseline period), have a frequency of at least 15 headache days, of which at least 8 must have the features of migraine headache (see definitions in Table CGAI.2). **To avoid biased reporting, patients must not be told the number of migraine headache days on which study qualification is based.**

[6] From Visit 2 to Visit 3 (prospective baseline period), have at least one headache-free day.

[7] From Visit 2 to Visit 3 (prospective baseline period), must achieve sufficient compliance with ePRO daily headache entries as demonstrated by completion of at least 80% of daily diary entries.

Informed Consent and Patient Agreements

[8] Are able and willing to give signed informed consent.

[9] Are reliable and willing to follow study procedures, including all follow-up visits.

[10] Women of child-bearing potential must test negative for pregnancy at the time of enrollment based on a serum pregnancy test.

[11] All patients, male and female, must agree to use a reliable method of birth control during the study as well as for 5 months after the last dose of investigational product. Acceptable methods of birth control for this study include: oral contraceptives; implantable contraceptives; injectable contraceptives; a contraceptive patch; barrier methods such as diaphragms with contraceptive jelly, cervical caps with contraceptive jelly, condoms with contraceptive foam, or intrauterine devices; a partner with vasectomy. Birth control is not required if the female is infertile due to surgical sterilization (at least 6 weeks after surgical bilateral oophorectomy, hysterectomy, or at least 6 weeks after tubal ligation) confirmed by medical history, or menopause. Menopause is defined as spontaneous amenorrhea for at least 12 months not induced by a medical condition, or spontaneous amenorrhea of 6-12 months and a follicle stimulating hormone level >40 mIU/mL.

[12] Agree not to post any personal medical data related to the study or information related to the study on any website or social media site (for example, Facebook, Twitter, LinkedIn, Google+, etc.) until the entire trial has completed.

5.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria at screening:

Prior/Concurrent Clinical Trial Experience

[13] Are currently enrolled in any other clinical trial involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.

[14] Have participated within the last 30 days or within 5 half-lives (whichever is longer) in a clinical trial involving an investigational product. If the investigational product's half-life is not known, 6 months should have passed prior to Visit 1.

[15] Current use or prior exposure to LY2951742 or another CGRP antibody, including those who have previously completed or withdrawn from this study or any other study investigating a CGRP antibody.

Prior/concomitant therapy

[16] Patients who are taking, or are expected to take, therapeutic antibodies during the course of the study (for example, adalimumab, infliximab, trastuzumab, bevacizumab, etc.). Prior use of therapeutic antibodies, other than antibodies to CGRP or its receptor, is allowed if that use was more than 12 months prior to Visit 2.

[17] Known hypersensitivity to multiple drugs, monoclonal antibodies or other therapeutic proteins, or to LY2951742.

[18] Are currently receiving a disallowed treatment for the prevention of migraine headaches (anything other than topiramate or propranolol). Patients must have discontinued such disallowed preventive migraine treatment at least 30 days prior to Visit 2. Botulinum toxin A and B that has been administered in the head or neck area must be discontinued at least 4 months prior to Visit 2. Patients who have been on a stable dose of either topiramate or propranolol for at least 2 months prior to Visit 2 may continue to take that preventive medication throughout the trial. Patients may only take one of these 2 allowed prophylactic medications during the trial, and the dose must remain stable throughout the double-blind treatment period.

[19] Failure to respond to 3 or more adequately dosed migraine preventive treatments from different classes (that is, maximum tolerated dose for at least 2 months). Failure to respond due to tolerability issues is not considered a treatment failure. Migraine preventive treatments are defined as Level A and Level B in Table 1 of the American Academy of Neurology's Evidence-based Guidelines Update: Pharmacologic Treatment for Episodic Migraine Prevention in Adults (Silberstein et al. 2012) as well as botulinum toxin A or B.

Diagnostics Assessments

[20] History of persistent daily headache, cluster headache or migraine subtypes including hemiplegic (sporadic or familial) migraine, ophthalmoplegic migraine, and migraine with brainstem aura (basilar-type migraine) defined by IHS ICHD-3 beta.

[21] History of headache other than migraine, tension type headache, or medication overuse headache, as defined by IHS ICHD-3 beta within 3 months prior to randomization.

[22] History of head or neck injury within 6 months prior to Visit 1.

[23] Patients with a history of traumatic head injury associated with significant change in the quality or frequency of their headaches should be excluded.

Medical Conditions

[24] Have ECGs showing abnormalities compatible with acute cardiovascular events and/or serious cardiovascular risk, including but not limited to a corrected QT (QTcB [Bazett's]) interval >470 msec for women and >450 for men, or have had myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass graft, or deep vein thrombosis/pulmonary embolism within 6 months of screening, or have planned cardiovascular surgery or percutaneous coronary angioplasty, or a lifetime history of stroke.

[25] Patients with a body mass index $\geq$40 kg/m^2.

[26] Any liver tests outside the normal range at Visit 1 that are clinically significant. Alanine aminotransferase (ALT) >2X upper limit of normal (ULN), or total bilirubin level (TBL) >1.5X ULN, or alkaline phosphatase (ALP) >2X ULN must be discussed and judged not clinically significant by Eli Lilly and Company (Lilly) Medical prior to enrollment.

[27] Evidence of significant active or unstable psychiatric disease by medical history, such as bipolar disorder, schizophrenia, personality disorders, or other serious mood or anxiety disorders. Note: Patients with major depressive disorder or generalized anxiety disorder whose disease state is considered stable and expected to remain stable throughout the course of the study, in the opinion of the investigator, may be considered for inclusion if they are not on excluded medications.

[28] Patients who, in the clinician's judgment, are actively suicidal and therefore deemed to be at significant risk for suicide, or those who have answered "yes" to either Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) or Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the "Suicidal Ideation" portion of the Columbia Suicide Severity Rating Scale (C–SSRS), or answer "yes" to any of the suicide-related behaviors (actual attempt, interrupted attempt, aborted attempt, preparatory act or behavior) on the "Suicidal Behavior" portion of the C–SSRS; and the ideation or behavior occurred within the past month.

[29] Women who are pregnant or nursing.

[30] Patients who have used opioids or barbiturate containing analgesic >3X per month for the treatment of pain in more than 2 of the past 6 months (opioid administration in an emergency setting may be an exception).

[31] History of drug or alcohol abuse/dependence within 1 year prior to Visit 1 (excessive or compulsive use as judged by the Investigator), or currently using drugs of abuse (including opioids, barbiturates and marijuana), or any prescribed or over-the-counter medication in a manner that the Investigator considers indicative of abuse/dependence.

[32] Have a positive urine drug screen for any substances of abuse at Visit 1. Note: A retest is allowed if the urine drug screen is positive for any prescribed substance or if, in the judgment of the investigator, there is an acceptable explanation for the positive result. The results of the retest must be negative at or prior to Visit 2.

[33] Have a history or presence of any other medical illness including but not limited to any autoimmune disease, cardiovascular, hepatic, respiratory, hematological, endocrine, psychiatric or neurological disease, or any clinically significant laboratory abnormality, that in the judgment of the investigator, indicates a medical problem that would preclude study participation.

Other Exclusions

[34] In the opinion of the investigator, have other issues which would interfere with compliance with the study requirements and completion of evaluations required for this study.

[35] Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

[36] Are Lilly employees.

[37] Are unwilling or unable to comply with the use of a data collection device.

5.3. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be considered for re-screen once, with approval from Lilly Medical for only the criteria shown below. The interval between screening and rescreening must be at least 45 days or longer if required for the specified timeframes in the inclusion/exclusion criteria or concomitant medication list. If rescreening is performed, the individual must sign a new ICF and will be assigned a new identification number.

- Inclusion criterion 1. If patients are less than age 18 at time of informed consent, they may be rescreened if they reach age 18 during the study enrollment period.
- Inclusion criterion 10
- Exclusion criterion 14
- Exclusion criterion 16
- Exclusion criterion 18
- Exclusion criterion 29

Patients using a concomitant medication that requires a stable dose for a specific duration prior to Visit 2 may be rescreened if additional time is needed to meet the duration requirement.

In addition, after consultation with and approval by a Lilly Medical representative, a patient may be rescreened if there is an unexpected technical difficulty with the electronic diary capture during the prospective baseline period.

5.4. Lifestyle and/or Dietary Requirements

No changes in lifestyle or dietary requirements are required during the study. However, patients must be in a fasting state for collection of laboratory samples at selected visits specified in Appendix 2.

6. Treatment

6.1. Treatments Administered

This study involves a comparison of LY2951742 (120 and 240 mg) administered once monthly with placebo. Sites will administer injections of LY2951742 or placebo at 3 office visits during the double-blind treatment phase and LY2951742 at 9 office visits during the open-label treatment phase (Appendix 2). During the double-blind treatment period, 2 injections of investigational product (LY2951742 and/or placebo) will be given at each dosing visit to preserve blinding.

Possible injection sites include the abdomen, thigh, and upper arm. Buttocks may also be used, if needed.

The investigator or his/her designee is responsible for the following:

- maintaining accurate records of investigational product dispensing
- at the end of the study returning all unused medication to Lilly, or its designee, unless the sponsor and sites have agreed all unused medication is to be destroyed by the site, as allowed by local law.

6.1.1. Medical Devices

The manufactured medical devices provided for use in the study are prefilled syringes.

6.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomized to double-blind treatment at Visit 3. Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). The IWRS will be used to assign double-blind investigational product to each patient. Site personnel will confirm that they have located the correctly assigned package by entering the confirmation number found on the package into the IWRS.

To achieve between-group comparability, the randomization will be stratified by country, acute headache medication overuse (yes/no), and use of concurrent migraine prophylactic medication (yes/no). Acute headache medication overuse will be determined during the prospective baseline period. Acute headache medication overuse criteria will be adapted from Section 8.2 of the ICHD-3 beta guidelines (ICHD-3 2013). To ensure an appropriate balance of patients with concomitant prophylaxis use, the sponsor will stop enrollment of patients with concomitant prophylaxis use if the number of patients exceeds approximately one-third.

6.2.1. Selection and Timing of Doses

The actual time of all dose administrations will be recorded in the patient's electronic case report form (eCRF).

6.3. Blinding

This is a double-blind study.

To preserve the blinding of the study, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete.

Emergency unblinding for AEs may be performed through the IWRS. This option may be used ONLY if the patient's well-being requires knowledge of the patient's treatment assignment. All unblinding events are recorded and reported by the IWRS.

If an investigator, site personnel performing assessments, or patient is unblinded, the patient must be discontinued from the study. In cases where there are ethical reasons to have the patient remain in the study, the investigator must obtain specific approval from a Lilly clinical research physician (CRP) or clinical research scientist (CRS) for the patient to continue in the study.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If an emergency unblinding occurs, Lilly must be notified as soon as possible.

6.4. Packaging and Labelling

LY2951742 and matching placebo (excipients only) will be supplied as an injectable solution in 1-mL, single-dose, prefilled, disposable manual syringes with study-specific labels during the double-blind treatment phase. Each syringe of LY2951742 is designed to deliver LY2951742 120 mg. The syringes (and contents) containing either LY2951742 or placebo will be visibly indistinguishable from each other. Syringes will be supplied in cartons, with the appropriate quantity of syringes specific to the planned dispensing schedule of the investigational product.

Clinical trial materials will be labeled according to the country's regulatory requirements.

6.5. Preparation/Handling/Storage

Investigational product will be shipped (as prefilled syringes) to sites using cold chain transportation. Investigational product must be stable and stored in a refrigerator at 2ºC to 8ºC (35.6ºF to 46.4ºF).

Approximately 30 minutes prior to administration, the syringe should be removed from the storage area and allowed to equilibrate at ambient conditions. The drug product should be kept away from direct exposure to bright light (such as sunlight) and hot surfaces until administration.

6.6. Dose Modification

Dose modifications are not permitted during the double-blind portion of this study. At the beginning of the open-label extension (Visit 7), all patients will be started at a dose of 240 mg LY2951742, then will receive a dose of 120 mg at Visit 8, with flexible dosing of 120 mg/month or 240 mg/month based on the discretion of the investigator at each visit thereafter.

6.6.1. Special Treatment Considerations

During open-label treatment (Study Period IV), patients on concurrent prophylaxis medication (stable dose of topiramate or propranolol) may now discontinue or modify the dose of that prophylaxis at the discretion of the investigator.

During the post-treatment phase (Study Period V), patients will not receive LY2951742 or placebo. One month after Visit 16, if clinically warranted due to a worsening of symptoms, patients may start migraine preventive medication(s) at the discretion of the investigator. Patients already on concurrent prophylaxis medication (stable dose of topiramate or propranolol) may add other prophylactic medication at that time. Initiation (or addition) of migraine preventive medications during the first month of the post-treatment follow-up phase are discouraged. The list of allowed preventive medications is provided separately.

6.7. Treatment Compliance

Investigators will be required to document the administration of investigational product in the eCRF.

Investigational product must be administered as indicated in the Schedule of Activities (Appendix 2). If the investigator is unable to administer the investigational product in the allowed window, the situation should be discussed with Lilly to determine if the patient may continue.

6.8. Concomitant Therapy

Table CGAI.3 contains the list of medications that are, and are not, allowed in this study. The concomitant use of acute medications to treat migraine is allowed, with some limitations. In general, treatments used for the prevention of migraine are not allowed at any time during Study Periods I through IV. However, the study will allow approximately one-third of enrolled patients to continue migraine prophylactic treatment with either topiramate or propranolol if the patient has been on a stable dose for at least 2 months prior to Visit 2 and if dosing will remain stable throughout the double-blind treatment period.

Table CGAI.3. Treatments Allowed and Treatments Not Allowed as Concomitant Therapy

Medications allowed for the ACUTE treatment of migraine headaches or other pain or injury: Acetaminophen (paracetamol), NSAIDs; Triptans; Ergotamine and derivatives; Isometheptene mucate, dichloralphenazone and acetaminophen combination (Midrin); or combinations thereof. The following medications are allowed with restrictions: 1. Opioid and barbiturates no more than 3 days/month (SP II, III and IV). 2. Single dose of injectable steroids allowed only once during the study, in an emergency setting (SP III and IV).

Table CGAI.3. Treatments Allowed and Treatments Not Allowed as Concomitant Therapy (continued)

Medications, Procedures or Devices not allowed for any reason/indication:

Acetazolamide
Acupuncture
Anticonvulsants/Antiepileptics (except topiramate if per protocol Section 6.8)
Antipsychotics
Beta-blockers (except propranolol if per protocol Section 6.8)
Botulinum toxin applied to head/neck area
Cannabis / Cannabinoids
Chiropractic procedures, physiotherapy, TENS or other electric devices on head and neck
Corticosteroids for oral use
Flunarizine
Herbals with anti-inflammatory effect (feverfew, willow bark, petasites/butterbur), herbals with sympathomimetic effect (ma huang, ephedra, bitter orange, synephrine) and herbals with catecholamine transmitter reuptake inhibition (St John's Wort)
Monoamine oxidase inhibitors (MAOIs)
Memantine
Serotonin 5HT2a/2c antagonists, e.g.: trazodone, nefazodone
Stimulants (prescription strength), e.g.: methylphenidate, dextroamphetamine, mixed amphetamine salts
Tizanidine
Therapeutic antibodies, e.g.: adalimumab, infliximab, trastuzumab, bevacizumab, etanercept, etc.
Tricyclic antidepressants (TCAs)
Triptans for prophylaxis of menstrual related migraine
Venlafaxine
Verapamil

Restricted medication during SP II and III: Use of the following medications for indications other than migraine prevention is allowed providing the dose is stable 2 months prior to Visit 2 and is expected to remain stable during Visit 2 through 7.

ACE inhibitors
Angiotensin receptor blockers (ARBs)
Benzodiazepines
Bupropion
Calcium-channel blockers (except verapamil and flunarizine)
Clonidine
Guanfacine
Mirtazapine
SSRIs/NRIs/SNRIs (other than venlafaxine)
Use of electric devices (i.e. TENS), physiotherapy, chiropractic procedures on low back and extremities

Restricted medication during SP II and III: Use of the following medications for indications other than migraine prevention is allowed:

Beta-blockers, ophthalmic
Cyclandelate
Cyproheptadine
Melatonin

During SP IV (Visit 7 through 16), use of the following medications for indications other than migraine prevention is allowed:

Table CGAI.3. Treatments Allowed and Treatments Not Allowed as Concomitant Therapy (continued)

During SP IV (Visit 7 through 16), use of the following medications for indications other than migraine prevention is allowed:

ACE inhibitors
Angiotensin receptor blockers (ARBs)
Benzodiazepines
Bupropion
Clonidine
Cyclandelate
Cyproheptadine
Guanfacine
Melatonin
Mirtazapine
SSRI/NRIs/SNRIs
TCAs
Use of electric devices (i.e. TENS), physiotherapy, chiropractic procedures on low back and extremities.

SP V (After Visit 16)

One month after Visit 16, if clinically warranted due to a worsening of symptoms, patients may start migraine prevention medications at the discretion of the investigator **with the exception of antipsychotics, cannabis and cannabinoids, MAOIs, memantine, serotonin 5HT2a/2c antagonists, and stimulants, which remain excluded.**

6.9. Treatment after Study Completion

6.9.1. Study Extensions

This study includes an open-label extension (Study Period IV).

6.9.2. Continued Access

Investigational product will not be made available to patients after conclusion of this study.

7. Discontinuation Criteria

Patients who discontinue the study or investigational product during the double-blind treatment phase (Study Period III) or open-label treatment (Study Period IV) will proceed immediately to Study Period V.

7.1. Discontinuation from Study Treatment

7.1.1. Permanent Discontinuation from Study Treatment

Discontinuation of the investigational product is required in cases of pregnancy.

Discontinuation of the investigational product for abnormal liver tests is required when a patient meets one of the following conditions and the event is at least possibly related to study drug:

- ALT or aspartate aminotransferase (AST) >8X ULN
- ALT or AST >5X ULN for more than 2 weeks
- ALT or AST >3X ULN and TBL >2X ULN or prothrombin time >1.5X ULN
- ALT or AST >3X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- ALP >3X ULN
- ALP >2.5X ULN and TBL >2X ULN
- ALP >2.5X ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Discontinuation of investigational product also is required in the following cases, if the event is at least possibly related to study drug:

- Serious allergic reaction to study drug
- Serious injection-site reaction
- Serious event of suicidality or depression
- Serious cerebrovascular event.

Patients who discontinue the investigational product early will have end-of-therapy (early termination) procedures performed as shown in the Schedule of Activities (Appendix 2) and are requested to proceed into the post-treatment phase.

7.1.2. Temporary Discontinuation from Study Treatment

Not applicable.

7.1.3. Discontinuation of Inadvertently Enrolled Patients

If the sponsor or investigator identify a patient who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the sponsor CRP/CRS and the investigator to determine if the patient may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor

CRP/CRS to allow the inadvertently enrolled patient to continue in the study with or without treatment with investigational product.

7.1.4. Permanent Discontinuation from the Study

Some possible reasons that may lead to permanent discontinuation include:

- Enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- Investigator Decision
    - the investigator decides that the patient should be discontinued from the study
    - if the patient, for any reason, requires treatment with a disallowed therapeutic agent that has been demonstrated to be effective for the study indication (prevention of migraine) during Study Period III (double-blind treatment), discontinuation from the study occurs prior to introduction of the new agent
- Subject Decision
    - the patient asks to be withdrawn from the study

Patients who discontinue the study early will have end-of-study (early termination) procedures performed as shown in the Schedule of Activities (Appendix 2) and are requested to proceed into the post-treatment phase.

7.1.5. Patients Lost to Follow-Up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

8. Study Assessments and Procedures

Appendix 2 lists the Schedule of Activities, with the study procedures and their timing (including tolerance limits for timing).

Appendix 3 lists the laboratory tests that will be performed for this study.

Appendix 4 lists the tests that may be obtained in the event of a treatment-emergent hepatic abnormality.

Unless otherwise stated in the subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

8.1. Efficacy Assessments

8.1.1. Primary Efficacy Assessments

ePRO Diary: Patients will be asked to use an ePRO device to record headache information, the name and dose of concomitant medications used for the acute treatment of migraine, and the use of other pain medications. Patients will use the ePRO system to report headaches, intensity of headache and headache features. The system also will be used to collect information about migraine-associated symptoms (for example, photophobia, phonophobia, nausea, and/or vomiting).

8.1.2. Secondary Efficacy Assessments

Secondary efficacy assessments in this study (Table CGAI.1) are intended to facilitate the collection and analysis of information such as onset of sustained effect, change in functioning, and changes in medication use for the acute treatment of migraine or headache. Much of this information will be provided by the ePRO system. Scales to be used for secondary efficacy assessments are summarized below.

8.1.2.1. Patient Global Impression of Severity

The Patient Global Impression of Severity (PGI-S) scale (Guy 1976) is a patient-rated instrument that measures baseline illness severity. The PGI-S includes a range of possible responses, from 1 ("normal, not at all ill") to 7 ("extremely ill").

8.1.2.2. Patient Global Impression of Improvement

The Patient Global Impression of Improvement (PGI-I) scale (Guy 1976) is a patient-rated instrument that measures the improvement of the patient's symptoms. It is a 7-point scale in which a score of 1 indicates that the patient is "very much better," a score of 4 indicates that the patient has experienced "no change," and a score of 7 indicates that the patient is "very much worse."

8.1.3. Appropriateness of Assessments

All efficacy and safety assessments have been well documented and are generally regarded as reliable, accurate, and relevant in this patient population. This includes health outcomes measures considered to be appropriate for evaluating changes in quality of life, global functioning, and disability (Section 8.9).

8.2. Adverse Events

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The investigator is responsible for the appropriate medical care of patients during the study.

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational product or the study, or that caused the patient to discontinue the investigational product before completing the study. The patient should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

After the ICF is signed, study site personnel will record via eCRF the occurrence and nature of each patient's pre-existing condition(s), including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record via eCRF any change in the condition(s) and any new condition(s) as AEs. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure or investigational product via eCRF.

The investigator will decide whether he or she interprets the observed AEs as reasonably possibly related to migraine headache, to the investigational product, study device, study procedure, or other concomitant treatment or pathologies.

The investigator will answer yes/no when making this assessment.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

If a patient's investigational product is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via eCRF, clarifying if possible, the circumstances leading to discontinuations of treatment.

8.2.1. Serious Adverse Events

An SAE is any AE from this study that results in one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason: important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious, based upon appropriate medical judgment.
- when a condition related to the investigational device (for example, prefilled syringe) necessitates medical or surgical intervention to preclude either permanent impairment of a body function or permanent damage to a body structure, the serious outcome of "required intervention" will be assigned.

Although all AEs after signing the ICF are recorded in the eCRF, SAE reporting begins after the patient has signed the ICF and has received investigational product. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product, it needs to be reported ONLY if it is considered reasonably possibly related to study procedure.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

Pregnancy (during maternal or paternal exposure to investigational product) does not meet the definition of an AE. However, to fulfill regulatory requirements, any pregnancy that occurs during the study, including those in which conception occurred within 5 months after last administration of investigational product, should be reported using the SAE process to collect data on the outcome for both mother and fetus.

Investigators are not obligated to actively seek AEs or SAEs in patients once they have discontinued and/or completed the study (the patient summary eCRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

8.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to investigational product or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidance or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the recording

and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidance.

8.2.1.2. Adverse Event Monitoring with a Systematic Questionnaire

Suicidality will be assessed as required by the US Food and Drug Administration's Division of Neurology for use in clinical trials involving all drugs for neurological indications. Before administering the C-SSRS (Posner et al. 2011), study site personnel will question the patient about any change in the pre-existing condition(s) and the occurrence and nature of any AEs. Nonserious AEs obtained through the questionnaire are recorded and analyzed separately. Only *serious* AEs and AEs leading to discontinuation elicited through the C-SSRS are to be recorded as AEs via eCRF. Serious adverse events must be reported to Lilly or its designee within 24 hours as SAEs. Any suicidal behavior, or suicidal ideation per items 4 or 5 (active suicidal ideation with some intent to act, either without specific plan or with specific plan and intent) would prompt referral of the patient to a mental health professional.

8.2.2. Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Patients will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product (or drug delivery system such as a prefilled syringe) so that the situation can be assessed.

8.3. Treatment of Overdose

No data are available at this stage of development.

8.4. Safety Assessments

8.4.1. Electrocardiograms

For each patient, a single, 12-lead digital ECG will be collected at the visits shown in the Schedule of Activities (Appendix 2). Electrocardiograms will have a central overread and should be recorded according to the study-specific recommendations included in the ECG manual.

Any clinically significant findings from ECGs that result in a diagnosis should be reported to Lilly or its designee as an AE via eCRF.

8.4.2. Vital Signs

Vital signs will include body temperature, blood pressure, and pulse. Blood pressure and pulse will be measured in triplicate in the sitting position prior to blood draws and study drug administration (see Study Schedule [Appendix 2]).

Any clinically significant findings from vital signs measurement that result in a diagnosis should be reported to Lilly or its designee as an AE via eCRF.

8.4.3. Laboratory Tests

For each patient, laboratory tests detailed in Appendix 3 should be conducted according to the Schedule of Activities (Appendix 2).

Any clinically significant findings from laboratory tests that result in a diagnosis should be reported to Lilly or its designee as an AE via eCRF.

In addition, an immunogenicity plasma sample will be collected, when possible, for any patient who experiences a potential systemic allergic/hypersensitivity reaction during the study as judged by the investigator. This immunogenicity plasma sample should be collected immediately or as soon as possible, taking into consideration the availability and wellbeing of the patient. Exact date and time of the sample should be recorded on the laboratory requisition form.

8.4.4. Other Tests

Not applicable.

8.4.5. Safety Monitoring

Investigators are responsible for monitoring individual patient safety throughout the trial. If a study patient/subject experiences elevated ALT ≥3X ULN, ALP ≥2X ULN, or elevated TBL ≥2X ULN, clinical and laboratory monitoring should be initiated by the investigator. Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient/subject safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP/CRS regarding collection of specific recommended clinical information and follow-up laboratory tests. See Appendix 4.

Neurological examinations will be conducted at screening, Month 3 , Month 6, Month 9, and Month 12 of treatment, as well as at the final visit of the follow-up period or early termination visit in order to assess for any signs of pre-existing or treatment-emergent neurological abnormalities such as stroke or other cerebrovascular events. If a study patient experiences signs of a cerebrovascular event, appropriate follow-up and clinical management should be conducted by the investigator, and the Lilly CRP/CRS should be consulted regarding collection of further clinical information and follow-up testing.

Lilly will periodically review evolving aggregate safety data within the study by appropriate blinded methods. In addition, safety data for the trial will also be reviewed periodically by an independent Data Monitoring Committee (DMC; an advisory group for this study formed to protect the integrity of data; refer to Interim Analyses section). In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, members of the DMC can request additional analyses of the safety data.

8.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Appendix 2), venous blood samples of approximately 2.5 mL each will be collected to determine the serum concentrations

of LY2951742. A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor.

When a blood sample is collected, the time and date of last dose administration prior to blood sampling should be recorded. The actual date and time (24-hour clock time) of each sampling will be recorded. LY2951742 concentration information that may/would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded. Bioanalytical samples collected to measure investigational product concentration will be retained for a maximum of 1 year following last patient visit for the study.

A validated assay will be used to determine serum LY2951742 concentrations. Samples will be analyzed at a laboratory approved by the sponsor.

It is intended that blood samples collected from patients who received placebo should not be analyzed for determination of serum concentrations of LY2951742.

8.6. Pharmacodynamics

At the visits and times specified in the Schedule of Activities (Appendix 2), venous blood samples will be collected to determine the plasma concentrations of CGRP. A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor. When a blood sample is collected, the time and date of last dose administration prior to blood sampling should be recorded. The actual date and time (24-hour clock time) of each sampling will be recorded.

A validated drug-tolerant assay will be used to determine plasma CGRP concentrations. Samples will be analyzed at a laboratory approved by the sponsor.

Plasma CGRP concentration information that may/would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Bioanalytical samples collected to measure CGRP will be identified by the patient number (coded) and retained for a maximum of 1 year following last patient visit for the study at a facility selected by the sponsor.

8.8. Biomarkers

Blood samples for non-genetic biomarker research will be collected at the times specified in the Schedule of Activities (Appendix 2), where local regulations and ERBs allow.

Samples will be used for research on the drug target, disease process, pathways associated with migraine headache and/or other pain conditions, mechanism of action of LY2951742, and/or research method or in validating diagnostic tools or assay(s) related to migraine headache and/or other pain conditions.

All biomarker samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the investigator site personnel. Samples will be destroyed according to a process consistent with local regulations.

Samples will be retained for a maximum 15 years after the last patient visit for the study, or for a shorter period if local regulations and ERBs impose shorter time limits, at a facility selected by the sponsor. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in drug development or when the drug is commercially available.

8.8.1. Samples for Immunogenicity Research

Where local regulations and ERBs allow, blood samples for immunogenicity testing will be collected to determine antibody production against LY2951742 as specified in the Schedule of Activities (Appendix 2). Immunogenicity will be assessed by a validated assay designed to detect anti-drug antibodies in the presence of the investigational product. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of LY2951742.

Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if regulations and ERBs impose shorter time limits, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to LY2951742.

8.9. Health Economics

Health economic, disability and quality of life assessments of LY2951742 in patients with migraine will be based on the following scales:

Migraine Disability Assessment Scale (MIDAS): The MIDAS was designed to quantify headache-related disability over a 3-month period. This instrument consists of five items that reflect the number of days reported as missing, or with reduced productivity at work or home and social events; higher values are indicative of more disability (Stewart 1999; Stewart 2001). This instrument is considered highly reliable and valid; and is correlated with clinical judgment regarding the need for medical care (Stewart 1999; Stewart 2001).

Migraine-Specific Quality of Life questionnaire (MSQ v2.1): The MSQ v2.1 is a self-administered health status instrument, and was developed to address physical and emotional limitations of specific concern to individuals suffering from migraine headaches. The instrument consists of 14 items that address 3 domains: (1) Role Function-Restrictive; (2) Role Function-Preventive; and, (3) Emotional Function (Jhingran 1998). The instrument was designed with a 4-week recall period, and is considered reliable, valid and sensitive to change in migraine (Jhingran 1998; Rendas-Baum 2013). Clinically meaningful differences for each domain have been established and are widely used in the literature.

Health Care Resource Utilization (HCRU) and Employment Status: The HCRU will be solicited by study personnel while documenting patient responses. The HCRU consists of 3 questions, asking about hospital emergency room visits, overnight stays in a hospital, and any other visits with a healthcare professional that occurred since their last study visit. Patients are also specifically asked about the number of health care events that are related to migraine headaches, outside of visits associated with their participation in the clinical trial. The baseline visit will include the same questions, however with the frame of reference being over the last 6 months. A question on employment status is also solicited, given the correlation and potential confounding with health outcomes measures.

9. Statistical Considerations and Data Analysis

9.1. Determination of Sample Size

The study will screen an estimated 1833 potential study participants to ensure a minimum of approximately 825 patients. Based on the assumption of an effect size of 0.33 and a dropout rate of approximately 15%, the minimum sample size of 825 provides more than 90% power that at least 1 dose of LY2951742 will separate from placebo at a two-sided significance level of 0.05 based on simulations using Dunnett (Dunnett 1955) test. The 825 patients will be randomized in a 2:1:1 ratio to placebo (target of 413 patients), 120 mg/month of LY2951742 (target of 206 patients), or 240 mg/month (target of 206 patients), with the opportunity to increase the final sample size at an interim analysis if indicated to maintain a well-powered study. To preserve blinding, details of the sample size and power calculations are omitted from this protocol and are provided to the ERB in a separate document.

Approximately 100 sites in 11 countries are planned for inclusion in Study CGAI, with an average of approximately 8 patients to be randomized at each investigative site. The final number of sites, countries, and patients per site may vary depending on sites' enrollment rates and whether sample size is increased to maintain power.

9.2. General Statistical Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. Details of statistical analysis methods will be described in the statistical analysis plan (SAP) document.

Unless otherwise specified, analyses will be conducted on an intent-to-treat (ITT) population, which will include all patients who are randomized and receive at least one dose of investigational product. Patients in the ITT population will be analyzed according to the treatment group to which they are randomized. When change from baseline is assessed, the patient will be included in the analysis only if he/she has a baseline and a postbaseline measurement.

Randomization will be stratified based on the frequency of acute headache medication intake during the 30-day baseline as yes/no overuse of acute headache medications. In addition, concomitant prophylaxis use will also be stratified.

For some of the analyses of the open-label treatment phase (Study Period IV), the open-label treatment population will be used. Open-label treatment population will be defined as all patients who entered the open-label treatment phase as indicated by receiving study drug at Visit 7. Patients in the open-label treatment population will be analyzed according to the treatment to which they were randomized in the double-blind period (Study Period III), as appropriate.

The primary analyses will be performed using a restricted maximum likelihood-based mixed models repeated measures (MMRM) technique with prespecified model terms (Section 9.4.1).

Visitwise binary efficacy variables will be analyzed using a generalized linear mixed model (GLIMMIX) as pseudo-likelihood-based mixed effects repeated measures analysis.

In addition to the MMRM approach, analysis of covariance (ANCOVA) model or analysis of variance (ANOVA) with the last-observation-carried-forward (LOCF) will also be implemented. When an ANCOVA model is used to analyze a continuous variable, the model will contain the main effects of treatment and pooled country, baseline medication overuse (yes/no), concomitant prophylaxis use (yes/no), as well as the continuous fixed covariates of baseline. The ANOVA model will use the same terms except the continuous fixed covariates of baseline. Type III sum-of-squares for the least-squares means will be used for the statistical comparisons.

Continuous efficacy and health outcome endpoints will be analyzed using MMRM methods, as well as an ANCOVA model with LOCF imputation if deemed appropriate.

Categorical comparisons between treatment groups will be performed using Cochran-Mantel-Haenszel (CMH) controlling for pooled country and using Fisher's exact test, where appropriate.

Countries will be pooled as deemed necessary for statistical analysis purposes.

Treatment effects will be evaluated based on a 2-sided significance level of 0.05 for all the efficacy and safety analyses unless otherwise stated. The 95% confidence intervals for the difference in least-square means between treatment groups will be presented. Adjustments for multiple comparisons for the analyses corresponding to the primary and secondary objectives for potential label inclusion are described in the sections on the primary and secondary efficacy analyses below. There will be no adjustments for multiplicity for analyses of other data.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report or SAP. Additional exploratory analyses of the data will be conducted as deemed appropriate.

9.3. Treatment Group Comparability

9.3.1. Patient Disposition

The number and percentage of ITT patients who complete the study or discontinue early will be tabulated for all treatment groups for double-blind treatment (Study Period III), open-label treatment (Study Period IV), and post-treatment follow-up (Study Period V) both overall and by visit. Patient allocation by investigator will be summarized for Study Period III for all ITT patients. Patient allocation by investigator will also be listed for all study periods.

9.3.2. Patient Characteristics

The following patient characteristics at baseline will be summarized by treatment group for all ITT patients.

- Demographic (age, gender, ethnic origin, height, weight, body mass index)
- Migraine headache, headache, variation of migraine/headache measures per 30-day baseline period

- Alcohol, tobacco, caffeine and nicotine consumption
- Medical history and preexisting condition
- Medication overuse

Medical history and pre-existing conditions will be summarized by preferred term within system organ class (SOC).

9.3.3. Concomitant Therapy

The proportion of patients who received concomitant medication collected from eCRF as well as abortive medications collected through ePRO will be summarized for all ITT patients for the double-blind, open-label, and post-treatment phases separately.

9.3.4. Treatment Compliance

Not applicable.

9.3.5. Electronic Patient-reported Outcome Diary Compliance

ePRO dairy compliance at each 1-month period, including baseline, will be calculated. Diary compliance at each period is calculated as:

$$\frac{\text{Actual number of diary days in the period}}{\text{Expected number of diary days in the period}} * 100$$

9.4. Primary and Secondary Analyses

9.4.1. Primary Analyses

The primary efficacy measure is the overall mean change from the baseline period in the number of monthly migraine headache days during the 3-month double-blind treatment phase, and the primary analysis will evaluate the efficacy of LY2951742 (120 or 240 mg/month) compared with placebo.

The primary analysis will be performed using a restricted maximum likelihood-based MMRM technique. The analysis will include the fixed categorical effects of treatment, pooled country, medication overuse (yes/no), concomitant prophylaxis use (yes/no), month, and treatment-by-month interaction, as well as the continuous fixed covariates of baseline number of migraine headache days and baseline number of migraine headache days-by-month interaction.

An unstructured covariance structure will be used to model within-patient errors. The Kenward-Roger (Kenward and Roger 1997) approximation will be used to estimate denominator degrees of freedom. If the model does not converge with both the Hessian and the G matrix being positive definite under the default fitting algorithm used by PROC MIXED, the Fisher scoring algorithm will be implemented by specifying the SCORING option in SAS. If the model still

fails to converge, the model will be fit using covariance matrices of the following order specified by a decreasing number of covariance parameters until convergence is met:

- Heterogeneous Toeplitz
- Heterogeneous First-order autoregressive
- Toeplitz
- First-order autoregressive

When the unstructured covariance matrix is not utilized, the sandwich estimator (Diggle and Kenward 1994) will be used to estimate the standard errors of the fixed effects parameters. The sandwich estimator is implemented by specifying the EMPIRICAL option in SAS®. When the sandwich estimator is utilized, the Kenward-Roger approximation for denominator degrees of freedom cannot be used. Instead, the denominator degrees of freedom will be partitioned into between-subject and within-subject portions by the DDFM=BETWITHIN option in SAS®. SAS® PROC MIXED will be used to perform the analysis.

If the sample size is increased as a result of the interim analysis, the Cui, Hung, and Wang (CHW) procedure (Cui et al. 1999) will be applied to the primary endpoint to control the type I error at a one sided α=0.025 significance level. The CHW method ensures strong control of type 1 error when the sample size is increased in a data dependent manner.

If the sample size is increased as a result of the interim analysis, an unadjusted point estimate for the primary efficacy analysis will be calculated and reported. A median unbiased point estimate and a stage-wise adjusted confidence interval for the primary efficacy analysis will be calculated and reported based on the approach described by Brannath and colleagues (Brannath et al. 2009) to assess sensitivity of the point estimate.

9.4.2. Key Secondary Analyses

The key secondary objectives (see Table CGAI.1) will be tested using an appropriate multiple testing approach providing strong control of the familywise error rate (for the primary and key secondary tests) at a one-sided 0.025 alpha level (or, equivalently, two-sided 0.05 alpha level).

There will be no adjustments for multiplicity for analyses of other endpoints. If the multiple testing approach for key secondary measures only needs to be changed, the updated approach will be provided in the SAP, and it should not lead to modification of this protocol.

The key secondary measures will be analyzed for the double-blind treatment (Study Period III).

For the continuous key secondary measures, the change from baseline will be analyzed from repeated measures analyses as described in Section 9.4.1. For the categorical key secondary efficacy measure of 50%, 75%, and 100% response, the percentage of patients meeting response criteria during the 3-month double-blind treatment phase will be estimated for each treatment from a categorical, pseudo-likelihood-based repeated measures analysis of longitudinal binary

outcomes indicating whether patients meet response criteria. This analysis will be implemented using the GLIMMIX procedure in SAS.

If the sample size is increased, the CHW test statistic will be calculated for the primary and all the key secondary outcomes before applying the multiple testing procedure.

9.4.3. Other Secondary and Tertiary Efficacy Analyses

The other secondary and exploratory efficacy analyses will be conducted for the double-blind treatment, open-label treatment, and post-treatment phases.

For the continuous secondary and exploratory efficacy measures, the change from baseline to each 1-month period postbaseline measure will be analyzed from repeated measures analyses as described in Section 9.4.1.

In addition to the repeated measures analyses, the mean change from baseline to LOCF endpoint for each treatment will be estimated for the continuous efficacy measures using ANCOVA models as described in Section 9.2. Categorical analyses will use the same model as described in Section 9.4.2 (additional details are described in the SAP).

9.5. Safety Analyses

The safety analyses will be conducted for the double-blind treatment, open-label treatment, and post-treatment follow-up phases.

The safety and tolerability of treatment will be assessed by summarizing the following:

- adverse events
  - treatment-emergent adverse events (TEAEs)
    - by preferred term
    - by SOC
    - by maximum severity
    - by outcome
    - considered to be related to investigational product by investigator
  - serious adverse event
  - adverse event leading to discontinuation
- Suicidal ideation and behaviors assessed by solicited questioning using the C-SSRS
- Vital signs and weight
- electrocardiograms
- Laboratory measurements
- Anti-LY2951742 antibody

9.5.1. Categorical Safety Variables

Unless specified otherwise, the categorical safety analyses will include both scheduled and unscheduled visits.

Comparisons between treatment groups for all categorical safety measures will be made using the Fisher's exact test for Study Period III (double-blind treatment) with the ITT population.

9.5.2. Adverse Events

Treatment-emergent adverse events are defined as the reported AEs that first occurred or worsened during the postbaseline phase compared with baseline phase. For each TEAE, the severity level of the event (mild, moderate, or severe) will be determined by patient or physician opinion. The Medical Dictionary for Regulatory Activities (MedDRA) Lowest Level Term will be used in the treatment-emergent computation. For each Lowest Level Term, the maximum severity at baseline will be used as the baseline severity. If the maximum severity during postbaseline is greater than the maximum baseline severity, the event is considered to be treatment-emergent for the specific postbaseline period. For each patient and TEAE, the maximum severity for the MedDRA level being displayed (Preferred Term, High Level Term, or SOC) is the maximum postbaseline severity observed from all associated Lowest Level Terms mapping to that MedDRA level.

For events that are gender-specific, the denominator and computation of the percentage will include only patients from the given gender.

9.5.3. Suicide-Related Thoughts and Behaviors

Suicidal ideation, suicidal behavior, and non-suicidal self-injurious behavior based on the C-SSRS will be summarized by treatment group. For each of the following events, the number and percentage of patients with the event will be enumerated by treatment: completed suicide, non-fatal suicide attempt, interrupted attempt, aborted attempt, preparatory acts or behavior, active suicidal ideation with specific plan and intent, active suicidal ideation with some intent to act without specific plan, active suicidal ideation with any methods (not plan) without intent to act, non-specific active suicidal thoughts, wish to be dead, and non-suicidal self-injurious behavior.

In addition, the number and percentage of patients who experienced at least one of the composite measures during Study Period III, Study Period IV, and Study Period V separately will be presented and compared. These include suicidal acts (completed suicide and nonfatal suicidal attempts), suicidal behavior (suicidal acts, interrupted attempts, aborted attempts, and preparatory acts or behavior), treatment-emergent suicidal ideation or treatment-emergent suicidal behavior.

The Fisher's exact test will be used for treatment comparisons.

9.5.4. Vital Signs and Weight

Vital signs collected during the study include systolic and diastolic blood pressure, pulse, and temperature. Blood pressure and pulse measurements will be taken when the patient is in a sitting position. Three measurements of sitting blood pressure and pulse will be collected. The 3 sitting blood pressure and pulse measurements will be averaged and used as the value for that visit for analysis.

The incidence rates of patients with treatment-emergent vital sign and weight changes based at any time postbaseline and at LOCF endpoint will be assessed using Fisher's exact test. Specific criteria for treatment emergent definition will be documented in the SAP.

9.5.5. Electrocardiogram Intervals and Heart Rate

Analyses of corrected QT interval will be calculated using two correction formulas. The QTcF (measured in milliseconds [msec]) will be calculated with Fridericia's formula as $QT/RR^{1/3}$. The Lilly Large Clinical Trial Population Based QT Correction (QTcR) (msec) will be calculated with the formula as $QT/RR^{0.413}$. The number and percent of patients meeting criteria for treatment-emergent abnormalities in ECG intervals (pulse rate [PR], QRS, QTcF, and QTcR) and heart rate at any time during study will be summarized. Treatment group comparisons will be performed using the Fisher's exact test.

9.5.6. Laboratory Tests

The incidence rates of patients with treatment-emergent abnormal, high, or low laboratory values at any time postbaseline and at LOCF endpoint will be assessed using the Fisher's exact tests for each laboratory test.

Patients will be defined as having a treatment-emergent low value if they have all normal or high values at baseline, followed by a value below the lower reference limit at any postbaseline visit. Patients with all normal or high values at baseline (no low values) will be included in the analysis of treatment-emergent low laboratory values. Patients will be defined as having a treatment-emergent high value if they have all normal or low values at baseline, followed by a value above the upper reference limit at any postbaseline visit. Patients with all normal or low values at baseline (no high values) will be included in the analysis of treatment-emergent high laboratory values.

For analytes simply classified as normal or abnormal, patients will be defined as having a treatment-emergent abnormal value if they have all normal values at baseline, followed by an abnormal value at any postbaseline visit. Patients with all normal values at baseline will be included in the analysis of treatment-emergent abnormal laboratory values.

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9.7. Other Analyses

9.7.1. Health Economics

The change from baseline for the double-blind treatment phase and for the open-label treatment and post-treatment follow-up phases for MSQ v2.1 (Role Function-Restrictive, Role Function-Preventive, Emotional Function, and total score) and MIDAS (item scores and total score) will be analyzed. In addition, categorical analyses will be performed. Changes in healthcare resource utilization and employment status will also be evaluated. Details are summarized in the SAP.

9.7.2. Immunogenicity Analysis

Refer to the SAP for details.

9.7.3. Subgroup Analyses

Subgroup analyses will be performed for primary efficacy measure (change from baseline on number of migraine headache days) separately for each of the subgroup populations listed in Table CGAI.4. Subgroup analyses will be conducted only for the ITT patients in Study Period III.

Each of the subgroup analyses for the primary measure of change from baseline in the number of migraine headache days will be conducted using MMRM. The same MMRM model described in Section 9.4.1 will be used with terms of subgroup, subgroup-by-treatment, subgroup-by-month, and subgroup-by-treatment-by-month interactions added as additional covariates.

Table CGAI.4. Definition of Subgroup Variables

Subgroup Variable	Categories
• Sex	Male, female
• Racial Origin (combine those with less than 10%)	American Indian / Alaskan Native Asian Black / African American Native Hawaiian / Pacific Islander White Multiple
• Ethnicity	Hispanic or Latino Not Hispanic or Latino
• Region	North America, Europe, Other
• Treatment-resistant status	Treatment-resistant status about whether a patient has failed 2 or more prophylactic treatments (Yes or No)
• Concurrent preventive treatment use	Yes or No
• Medication overuse	Yes versus No
• Having aura or not (during baseline period)	Yes or No
• Baseline anti-drug antibody status	Any confirmed positive anti-drug antibody at baseline (Yes versus No)
• Neutralizing anti-drug antibody status	Any positive neutralizing anti-drug antibody time point (Yes versus No) – note that neutralizing anti-drug antibody assays are performed only on confirmed-positive anti-drug antibodies.
• Treatment-emergent anti-drug antibody status	Any treatment-emergent anti-drug antibody (Yes versus No)

9.8. Interim Analyses

Two interim analyses are planned for this trial. The first interim analysis will occur during Study Period III (double-blind treatment); this may result in increasing the sample size or stopping the trial for futility. Details will be documented in the Statistical Analysis Center SAP, the ERB supplement and the DMC Charter.

The second interim analysis will be conducted after all patients have had the opportunity to complete Study Period III, and thus will be the final analysis of the primary efficacy endpoint.

To minimize the potential bias that results from performing an interim analysis, the first interim analysis for this study will be conducted under the auspices of an independent Statistical Analysis Center and DMC.

Only the DMC is authorized to evaluate unblinded interim efficacy and safety analyses (prior to the completion of the double-blind treatment phase). Study sites will receive information about interim results ONLY if they need to know for the safety of their patients.

Additional interim analyses may be conducted in support of regulatory submissions if necessary.

Unblinding details are specified in the unblinding plan section of the SAP or a separate unblinding plan document.

10. Study Governance Considerations

10.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

10.1.1. Informed Consent

The investigator is responsible for ensuring:

- that the patient understands the potential risks and benefits of participating in the study
- that informed consent is given by each patient. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of investigational product.
- answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial.

10.1.2. Ethical Review

The investigator must give assurance that the ERB was properly constituted and convened as required by International Conference on Harmonisation (ICH) guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF, including any changes made by the ERBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on GCP.

The study site's ERB(s) should be provided with the following:

- the current IB and updates during the course of the study
- informed consent form
- relevant curricula vitae

10.1.3. Regulatory Considerations

This study will be conducted in accordance with:

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- applicable ICH GCP guidelines
- applicable laws and regulations

Some of the obligations of the sponsor will be assigned to a third-party organization (TPO).

10.1.4. Investigator Information

Investigators in this clinical trial should be neurologists, headache specialists, or other specialists with experience in headache clinical trials and treating migraine headache patients.

10.1.5. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

10.1.6. Final Report Signature

The clinical study report (CSR) coordinating investigator will sign the final CSR for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

An investigator selected by the study team will serve as the CSR coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the CSR coordinating investigator.

The sponsor's responsible medical officer and statistician will approve the final CSR for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

10.2. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the eCRFs, and study procedures.
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail/e-mail, telephone, and/or fax
- review and evaluate eCRF data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its representatives, and/or by regulatory agencies at any time. Investigators will be given notice before an audit occurs.

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the investigator will keep records of ECGs, laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study according to retention requirements as outlined by the ICH guidelines. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

10.2.1. Data Capture System

An electronic data capture system will be used in this study. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system.

Some or all of a patient's data will be directly entered into the eCRF at the time that the information is obtained. In instances where direct data entry is not used, the site will maintain source documentation in the trial files, and the patient's data will be transcribed into the eCRF. Any data for which the eCRF will serve as the source document, or any other data not entered directly into the eCRF, will be identified and documented by the site in the site's trial file. For data handled by a data management TPO, eCRF data and some or all data that are related will be managed and stored electronically in the TPO system. Subsequent to the final database lock, validated data will be transferred to the sponsor. For data handled internally, eCRF data and some or all data that are related will be managed by the sponsor and stored electronically in the sponsor's system.

In this study, patient migraine headache data will be collected directly via an ePRO diary as part of an ePRO/Clinical Outcome Assessment (COA) system. Patient-rated scales/questionnaires will be collected directly via an ePRO tablet device at each visit. Data entered into the ePRO/COA system will serve as the source data.

If ePRO/COA records are stored at a third-party site, investigator sites will have continuous access to the source documents during the study and will receive an archival copy at the end of the study for retention.

Any data for which the ePRO/COA instrument record will serve to collect source data will be identified and documented by each site in that site's study file.

Case report form data will be encoded and stored in a clinical trial database. Data managed by a central vendor, such as laboratory test data or ECG data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly data warehouse. Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

10.3. Study and Site Closure

10.3.1. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly or its designee, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

10.3.2. Discontinuation of the Study

The study will be discontinued if Lilly or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

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Appendix 1. Abbreviations and Definitions

Term	Definition
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
ePRO	electronic patient-reported outcomes
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
ITT	intent to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWRS	interactive web-response system
SAE	serious adverse event
TEAE	treatment-emergent adverse event: Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with this treatment.

Appendix 2. Schedule of Activities

Schedule of Activities, Protocol I5Q-MC-CGAI (Double-Blind Treatment Phase)

Study Period (SP)	SP I Screening	SP II Prospective Baseline	SP III Double-Blind Treatment				
(Target) Interval (days) since previous visit			30-45	14	16	30	30
Allowable range (days) between visits	3-45	30-40[a]					
Interval allowance (days)				+/- 1	+/- 3	+/- 2	+/- 2
Visit	1	2	3	4[b]	5	6	7
Month			0	0.5	1	2	3
Assessments and Procedures							
Informed consent	X						
Inclusion/exclusion	X	X	X				
Demographics	X						
Physical examination	X						
Neurological examination[c]	X						X
Height	X						
Weight	X						X
Waist/hip circumference	X						
Medical history	X						
Pre-specified migraine history		X					
Substance use	X						
ECG[d]	X		X				X
Vital signs[e]	X		X		X	X	X
Adverse events	X	X	X	X	X	X	X
Concomitant medications	X	X	X		X	X	X
ePRO training		X					
ePRO daily patient entries		X	X	X	X	X	X
Patient training video			X				

Clinical Laboratory Tests and Sampling Schedule							
Hematology	X		X				X
Clinical chemistry	X		X[f]				X[f]
HDL	X		X[e]				X[e]
HbA1c			X				X
Fasting insulin/ fasting C-peptide			X[e]				X[e]
Urinalysis[g]	X		X				X
Serum Pregnancy (for women of childbearing potential) or FSH at V1 (all other female patients)[h]	X						X
Urine pregnancy[h]			X		X	X	
Urine drug screen	X						
Immunogenicity[i]			X	X	X	X	X
Biomarker storage sample[i]	X	X	X		X		
CCI							
PK blood sample[i]				X	X	X	X
CCI							
RNA			X				X
Study drug administered[j]			X		X	X	X (if continuing to OLE)
Scales, Questionnaires, and Outcome Measures							
MIDAS			X				X
MSQv2.1			X		X	X	X
HCRU/Employment Status			X		X	X	X
Non-migraine chronic pain assessment[k]			X				X
PGI-S			X		X	X	X
PGI-I					X	X	X
C-SSRS/SHSF, SHFU [l]	X	X	X		X	X	X

Schedule of Activities, Protocol I5Q-MC-CGAI (Open-Label and Post-Treatment Phases)

Study Period (SP)	SP IV Open-Label									SP V Post-treatment		
(Target) Interval (days) since previous visit	30	30	30	30	30	30	30	30	30	60	60	ET
Interval allowance (days)	+/- 2	+/- 2	+/- 2	+/- 2	+/- 2	+/- 2	+/- 2	+/- 2	+/- 2	+/- 5	+/- 5	
Visit	8	9	10	11	12	13	14	15	16	17	18	
Month	4	5	6	7	8	9	10	11	12	14	16	
Assessments and Procedures												
Weight			X			X			X		X	X
Neurological examination[c]			X			X			X		X	X
ECG[d]			X						X		X	X
Vital signs[e]	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
ePRO daily patient entries	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Tests and Sampling Schedule												
Hematology			X			X			X		X	X
Clinical chemistry			X[f]			X[f]			X[f]		X[f]	X[f]
HDL			X[f]			X[f]			X[f]		X[f]	X[f]
HbA1c			X			X			X		X	X
Fasting insulin/ fasting C-peptide			X[f]			X[f]			X[f]			X[f]
Urinalysis[g]			X			X			X		X	X
Serum Pregnancy (for women of childbearing potential)[h]									X		X	X

Study Period (SP)	SP IV Open-Label									SP V Post-treatment		
(Target) Interval (days) since previous visit	30	30	30	30	30	30	30	30	30	60	60	ET
Interval allowance (days)	+/- 2	+/- 2	+/- 2	+/- 2	+/- 2	+/- 2	+/- 2	+/- 2	+/- 2	+/- 5	+/- 5	
Visit	8	9	10	11	12	13	14	15	16	17	18	
Month	4	5	6	7	8	9	10	11	12	14	16	
Urine pregnancy[h]	X	X	X	X	X	X	X	X				
Immunogenicity[i]	X	X	X			X			X		X	X
Biomarker storage sample[i]			X						X		X	X
CCI												
PK blood sample[i]	X	X	X			X			X		X	X
Study drug[j]	X	X	X	X	X	X	X	X				
Scales, Questionnaires, and Outcome Measures												
MIDAS			X			X			X		X	X
MSQv2.1	X	X	X	X	X	X	X	X	X	X	X	X
HCRU/ Employment Status	X	X	X	X	X	X	X	X	X	X	X	X
Non-migraine chronic pain assessment[k]			X						X			X
PGI-S	X	X	X	X	X	X	X	X	X	X	X	X
PGI-I			X			X			X			X
C-SSRS/SHSF, SHFU[l]	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: CGRP = Calcitonin-gene related peptide; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ePRO = electronic patient reported outcome; ET = early termination; FSH = follicle stimulating hormone; HbA1c = hemoglobin A1C; HDL = high density lipoprotein; MIDAS = Migraine Disability Assessment test; MSQ (v2.1) = Migraine Specific Quality of Life Questionnaire; OLE = open-label extension; PGI-I = Patient Global Impression of Improvement; PGI-S = Patient Global Impression of Severity; PK = pharmacokinetics; RNA = ribonucleic acid; SHSF = Self-harm supplement form; SHFU = Self-harm follow-up form; V1 = Visit 1.

Note: Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with the Lilly, or its designee, clinical research physician. See Appendix 4 for more details regarding specific hepatic monitoring tests. If the patient has discontinued the trial and returns for hepatic follow-up, the site should use the 800 series as the visit designation.

[a] The eligibility period of the prospective baseline assessment will last from 30 to 40 days. Investigators and patients may have up to an additional 5 days to schedule their Visit 3 appointment (beyond the 40 days); however, eligibility will be based on the 30- to 40-day period.

[b] Visit is to include a review of any spontaneously reported adverse events and collection of blood samples for immunogenicity, PK, and CGRP plasma.

[c] A neurological exam will be conducted at screening, Month 3 (final visit of double-blind treatment), Months 6, 9, and 12 (open-label treatment), and Month 16/early termination in order to assess for any signs of pre-existing or treatment-emergent neurological abnormalities such as stroke or other cerebrovascular events.

[d] Electrocardiograms (ECGs) will be performed at Visit 1, Visit 3, Visit 7, Visit 10, Visit 16, and Visit 18 or early termination. Note: The Visit 3 ECG should be collected prior to blood draws and dosing. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

[e] Vital signs taken at every office visit will include body temperature, blood pressure and pulse. Blood pressure and pulse will be measured in triplicate in the sitting position and should be measured prior to blood draws. Blood pressure will be assessed by utilizing a calibrated machine.

[f] Chemistry labs collected at Visit 3, Visit 7, Visit 10, Visit 13, Visit 16, and Visit 18 or early termination must be fasting. Fasting is defined as no food or drink, except water, for at least 8 hours prior to testing.

[g] In the event of a positive urine leukocyte esterase result, a repeat urine sample will be collected and shipped to the central laboratory.

[h] A positive urine test must be followed by a serum pregnancy test for confirmation.

[i] Immunogenicity CCI and storage sample, and PK blood sampling to be performed at the indicated visits and prior to dose administration if the visit is a dosing visit. Samples will be taken in the event of early termination. Immunogenicity samples also may be collected in the event of a systemic allergic/hypersensitivity reaction (see Section 8.4.3). The exact date and time of the samples should be recorded.

[j] Patients will receive injections of placebo or LY2951742 after all other visit procedures are completed. Following the first double-blind dose at Visit 3 and the first open-label dose at Visit 7, patients will be observed for at least 30 minutes in the office.

[k] Questionnaire administered by clinician to assess other chronic pain conditions.

[l] The C-SSRS, and SHSF (and SHFU when applicable) will be completed at scheduled and unscheduled office visits.

Appendix 3. Clinical Laboratory Tests

Laboratory Tests Performed during the Study

Hematology:	**Clinical Chemistry:**[b]
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Mean cell volume	Total bilirubin
Mean cell hemoglobin concentration	Direct bilirubin
Leukocytes (WBC)	Alkaline phosphatase
Neutrophils, segmented	Alanine aminotransferase (ALT)
Lymphocytes	Aspartate aminotransferase (AST)
Monocytes	Blood urea nitrogen (BUN)
Eosinophils	Creatinine
Basophils	Uric acid
Platelets	Calcium
HbA_{1c}	Glucose (fasting)[b]
	Albumin
Urinalysis:	Creatine kinase (CK)
Specific gravity	Triglycerides
pH	Total cholesterol[b]
Protein	HDL[b]
Glucose	
Ketones	Insulin (fasting)
Blood	C-peptide (fasting)
Urine leukocyte esterase[a]	
Microscopic analysis[a]	CCI [redacted]
Urine culture[a]	PK Sample (LY2951742 serum concentration determination)
	Immunogenicity
	Urine Drug Screen[c]
	Pregnancy Test (females only)[c]
	Serum pregnancy or FSH
	Urine pregnancy test (local)
	Stored Samples
	Biomarker Storage
	CCI [redacted]
	RNA

Abbreviations: FSH = follicle-stimulating hormone; HbA1c = hemoglobin A1c; HDL = high density lipoprotein; PK = pharmacokinetic; RBC = red blood cells; RNA = ribonucleic acid; WBC = white blood cells.

[a] A positive urine leukocyte esterase result will require a follow-up sample with microscopic analysis and possibly a urine culture.

[b] Fasting laboratory samples will be collected as shown in the Schedule of Activities (Appendix 2). Fasting is defined as no food or drink, except water, for at least 8 hours prior to testing. All other samples may be collected on a nonfasting basis.

[c] May be repeated during the study at the discretion of the investigator.

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with the Lilly, or its designee, clinical research physician.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody[a]**
AST	**Alkaline phosphatase isoenzymes[a]**
GGT	**Anti-Actin antibody[a]**
CPK	**Anti-smooth muscle antibody[a]**

Abbreviations: ALT = alanine aminotransferase; AST = aspirate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

a Assayed by Lilly-designated or local laboratory.

b Reflex/confirmation dependent on regulatory requirements and/or testing availability.

Appendix 5. Protocol Amendment I5Q-MC-CGAI(a) Summary: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of LY2951742 in Patients with Chronic Migraine – the REGAIN Study

Overview

Protocol I5Q-MC-CGAI (A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of LY2951742 in Patients with Chronic Migraine – the REGAIN Study) has been amended. The new protocol is indicated by amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

The changes were required by 4 European Union Member States participating in the Voluntary Harmonisation Procedure. The key changes are as follows:

- Added the protocol amendment approval date (with updated trial alias) on every page of the protocol.
- Added language regarding the contents of each injection for the different treatment assignments in order to clarify how treatment is blinded (Section 4.1).
- Excluded patients with a prior lifetime history of stroke (Section 5.2, Exclusion [24]) to provide additional safeguards for patients who may be at risk for stroke.
- Added text to indicate that additional neurological examinations will be conducted to assess for possible cerebrovascular events, along with instructions for appropriate follow-up (Section 8.4.5, Safety Monitoring).
- Revised wording regarding procedures associated with emergency unblinding (Section 6.3) such that investigators no longer need to contact Lilly prior to emergency unblinding of a patient's treatment assignment.
- Added the list of allowed and disallowed concomitant treatments directly into Section 6.8 rather than referencing a separate document.
- Modified treatment discontinuation criteria (Section 7.1.1) to require (rather than recommend) discontinuation of treatment in the event of specific liver function test abnormalities, and added language to indicate the additional events requiring discontinuation from LY2951742 or placebo.
- Added assumptions of minimal sample size calculation (Section 9.1).
- Added information regarding the approximate number of countries, investigative sites, and patients planned for inclusion in the study (Section 9.1).
- [redacted]
- Added clarification on the statistical model to be used for subgroup analyses (Section 9.7.2).
- Updated the Schedule of Activities (Appendix 2) and footnotes to reflect added neurological examinations.

Revised Protocol Sections

Header

I5Q-MC-CGAI(a) Clinical Protocol

Footer

Approved: XX January 2016

Title

Protocol I5Q-MC-CGAI(a)

4. Study Design

4.1 Overview of Study Design

Study Period III: At the start of the 3-month double-blind treatment phase (Visit 3), patients meeting all eligibility requirements will be randomized to 1 of 3 treatment groups in a 2:1:1 ratio to receive placebo, 120 mg/month LY2951742, or 240 mg/month LY2951742, respectively. At Visit 3, if available and where local regulations and Ethical Review Boards allow, patients will also watch a training video designed to address patient expectations with regard to participation in a placebo-controlled trial and the difference between medical treatment and research. To preserve blinding throughout the study, patients in all treatment groups will receive 2 injections of investigational product at each dosing visit (two placebo injections, two 120-mg LY2951742 injections, or one placebo injection and one 120-mg injection). Patients randomised to the 120-mg dose of LY2951742 will receive an initial loading dose of 240 mg (2 injections of 120 mg each).

Patients will be given investigational product (LY2951742 or placebo) injections during office visits (Figure CGAI.1). For all treatment groups, investigational product is administered by subcutaneous injection once monthly at the dosing visits. At Visit 3 (first dose), patients are required to remain in the office for observation for 30 minutes post injection. Patients will continue to log in and complete the ePRO diary each day. Patients may continue to take their allowed acute migraine headache medication (with some limitations; see Section 6.8 ~~concomitant medications study tool~~) during the treatment phase.

Study Period V: Patients who discontinue from Study Period III or IV must enter directly into Study Period V for assessment during washout of investigational study drug. During this

4-month phase, sites and patients will continue to remain blinded to patients' original double-blind treatment assignments. Patients will follow all study procedures during Study Period V but will not receive investigational product. One month after Visit 16, if clinically warranted due to a worsening of symptoms, patients may start migraine prevention medication(s) at the discretion of the investigator (Section 6.6.1). The list of allowed preventive medications is provided in Section 6.8 ~~the concomitant medications study tool~~. At Visit 18 (Month 16), patients will return to the site for their last study visit and discharge from the study.

5. Study Population

5.2 Exclusion Criteria

Medical Conditions

[24] Have ECGs showing abnormalities compatible with acute cardiovascular events and/or serious cardiovascular risk, including but not limited to a corrected QT (QTcB [Bazett's])interval > 470 msec for women and >450 for men, or have had myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass graft, ~~stroke,~~ or deep vein thrombosis/pulmonary embolism within 6 months of screening, or have planned cardiovascular surgery or percutaneous coronary angioplasty, or a lifetime history of stroke.

6. Treatment

6.3 Blinding

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. ~~If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Lilly CRP/CRS prior to unblinding a patient's treatment assignment.~~ If an emergency unblinding occurs, ~~a patient's treatment assignment is unblinded,~~ Lilly must be notified as soon as possible ~~immediately~~.

6.8 Concomitant Therapy

Table CGAI.3 contains t~~T~~he list of medications that are, and are not, allowed in this study.~~or not allowed during the study can be found in the concomitant medications study tool.~~ The concomitant use of acute medications to treat migraine is allowed, with some limitations. ~~Any changes in the list of allowed/not allowed medications will be communicated to investigators and will not constitute a protocol amendment.~~ In general, ~~patients may not continue on a previous prophylactic migraine therapy~~treatments used for the prevention of migraine are not allowed at any time during Study Periods I through IV. However, the study will allow approximately one-

third of enrolled patients to continue migraine prophylactic treatment with either topiramate or propranolol if the patient has been on a stable dose for at least 2 months prior to Visit 2 and if dosing will remain stable throughout the double-blind treatment period.

Table CGAI.3. Treatments Allowed and Treatments Not Allowed as Concomitant Therapy

Medications allowed for the ACUTE treatment of migraine headaches or other pain or injury:

Acetaminophen (paracetamol), NSAIDs; Triptans; Ergotamine and derivatives; Isometheptene mucate, dichloralphenazone and acetaminophen combination (Midrin); or combinations thereof.

The following medications are allowed with restrictions:

1. Opioid and barbiturates no more than 3 days/month (SP II, III and IV).
2. Single dose of injectable steroids allowed only once during the study, in an emergency setting (SP III and IV).

Medications, Procedures or Devices not allowed for any reason/indication:

Acetazolamide
Acupuncture
Anticonvulsants/Antiepileptics (except topiramate if per protocol Section 6.8)
Antipsychotics
Beta-blockers (except propranolol if per protocol Section 6.8)
Botulinum toxin applied to head/neck area
Cannabis / Cannabinoids
Chiropractic procedures, physiotherapy, TENS or other electric devices on head and neck
Corticosteroids for oral use
Flunarizine
Herbals with anti-inflammatory effect (feverfew, willow bark, petasites/butterbur), herbals with sympathomimetic effect (ma huang, ephedra, bitter orange, synephrine) and herbals with catecholamine transmitter reuptake inhibition (St John's Wort)
Monoamine oxidase inhibitors (MAOIs)
Memantine
Serotonin 5HT2a/2c antagonists, e.g.: trazodone, nefazodone
Stimulants (prescription strength), e.g.: methylphenidate, dextroamphetamine, mixed amphetamine salts
Tizanidine
Therapeutic antibodies, e.g.: adalimumab, infliximab, trastuzumab, bevacizumab, etanercept, etc.
Tricyclic antidepressants (TCAs)
Triptans for prophylaxis of menstrual related migraine
Venlafaxine
Verapamil

Restricted medication during SP II and III: Use of the following medications for indications other than migraine prevention is allowed providing the dose is stable 2 months prior to Visit 2 and is expected to remain stable during Visit 2 through 7.

ACE inhibitors
Angiotensin receptor blockers (ARBs)
Benzodiazepines
Bupropion
Calcium-channel blockers (except verapamil and flunarizine)
Clonidine
Guanfacine

Mirtazapine
SSRIs/NRIs/SNRIs (other than venlafaxine)
Use of electric devices (i.e. TENS), physiotherapy, chiropractic procedures on low back and extremities

Restricted medication during SP II and III: Use of the following medications for indications other than migraine prevention is allowed:
Beta-blockers, ophthalmic
Cyclandelate
Cyproheptadine
Melatonin

During SP IV (Visit 7 through 16), use of the following medications for indications other than migraine prevention is allowed:

During SP IV (Visit 7 through 16), use of the following medications for indications other than migraine prevention is allowed:
ACE inhibitors
Angiotensin receptor blockers (ARBs)
Benzodiazepines
Bupropion
Clonidine
Cyclandelate
Cyproheptadine
Guanfacine
Melatonin
Mirtazapine
SSRI/NRIs/SNRIs
TCAs
Use of electric devices (i.e. TENS), physiotherapy, chiropractic procedures on low back and extremities.

SP V (After Visit 16)
One month after Visit 16, if clinically warranted due to a worsening of symptoms, patients may start migraine prevention medications at the discretion of the investigator **with the exception of antipsychotics, cannabis and cannabinoids, MAOIs, memantine, serotonin 5HT2a/2c antagonists, and stimulants, which remain excluded.**

7. Discontinuation Criteria

7.1. Discontinuation from Study Treatment

7.1.1. Permanent Discontinuation from Study Treatment

Discontinuation of the investigational product is required in cases of pregnancy.

Discontinuation of the investigational product for abnormal liver tests is required~~**should be considered** by the investigator~~ when a patient meets one of the following conditions and the event is at least possibly related to study drug~~after consultation with the Lilly designated medical monitor~~:

- ALT or aspartate aminotransferase (AST) >8X ULN
- ALT or AST >5X ULN for more than 2 weeks
- ALT or AST >3X ULN and TBL >2X ULN or prothrombin time >1.5X ULN
- ALT or AST >3X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- ALP >3X ULN
- ALP >2.5X ULN and TBL >2X ULN
- ALP >2.5X ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Discontinuation of investigational product also is required in the following cases, if the event is at least possibly related to study drug:

- Serious allergic reaction to study drug
- Serious injection-site reaction
- Serious event of suicidality or depression
- Serious cerebrovascular event.

8. Study Assessments and Procedures

8.4 Safety Assessments

8.4.5 Safety Monitoring

Neurological examinations will be conducted at screening, Month 3, Month 6, Month 9, and Month 12 of treatment, as well as at the final visit of the follow-up period or early termination visit in order to assess for any signs of pre-existing or treatment-emergent neurological abnormalities such as stroke or other cerebrovascular events. If a study patient experiences signs of a cerebrovascular event, appropriate follow-up and clinical management should be conducted by the investigator, and the Lilly CRP/CRS should be consulted regarding collection of further clinical information and follow-up testing.

9. Statistical Considerations and Data Analysis

9.1 Determination of Sample Size

The study will screen an estimated 1833 potential study participants to ensure a minimum of approximately 825 patients. Based on the assumption of an effect size of 0.33 and a dropout rate of approximately 15%, the minimum sample size of 825 provides more than 90% power that at least 1 dose of LY2951742 will separate from placebo at a two-sided significance level of 0.05 based on simulations using Dunnett (Dunnett 1955) test. The 825 patients will be randomized in a 2:1:1 ratio to placebo (target of 413 patients), 120 mg/month of LY2951742 (target of 206 patients), or 240 mg/month (target of 206 patients), with the opportunity to increase the final sample size at an interim analysis if indicated to maintain a well-powered study. To preserve blinding, details of the sample size and power calculations are omitted from this protocol and are provided to the ERB in a separate document.

Approximately 100 sites in 11 countries are planned for inclusion in Study CGAI, with an average of approximately 8 patients to be randomized at each investigative site. The final number of sites, countries, and patients per site may vary depending on sites' enrollment rates and whether sample size is increased to maintain power.

9.2 General Statistical Considerations

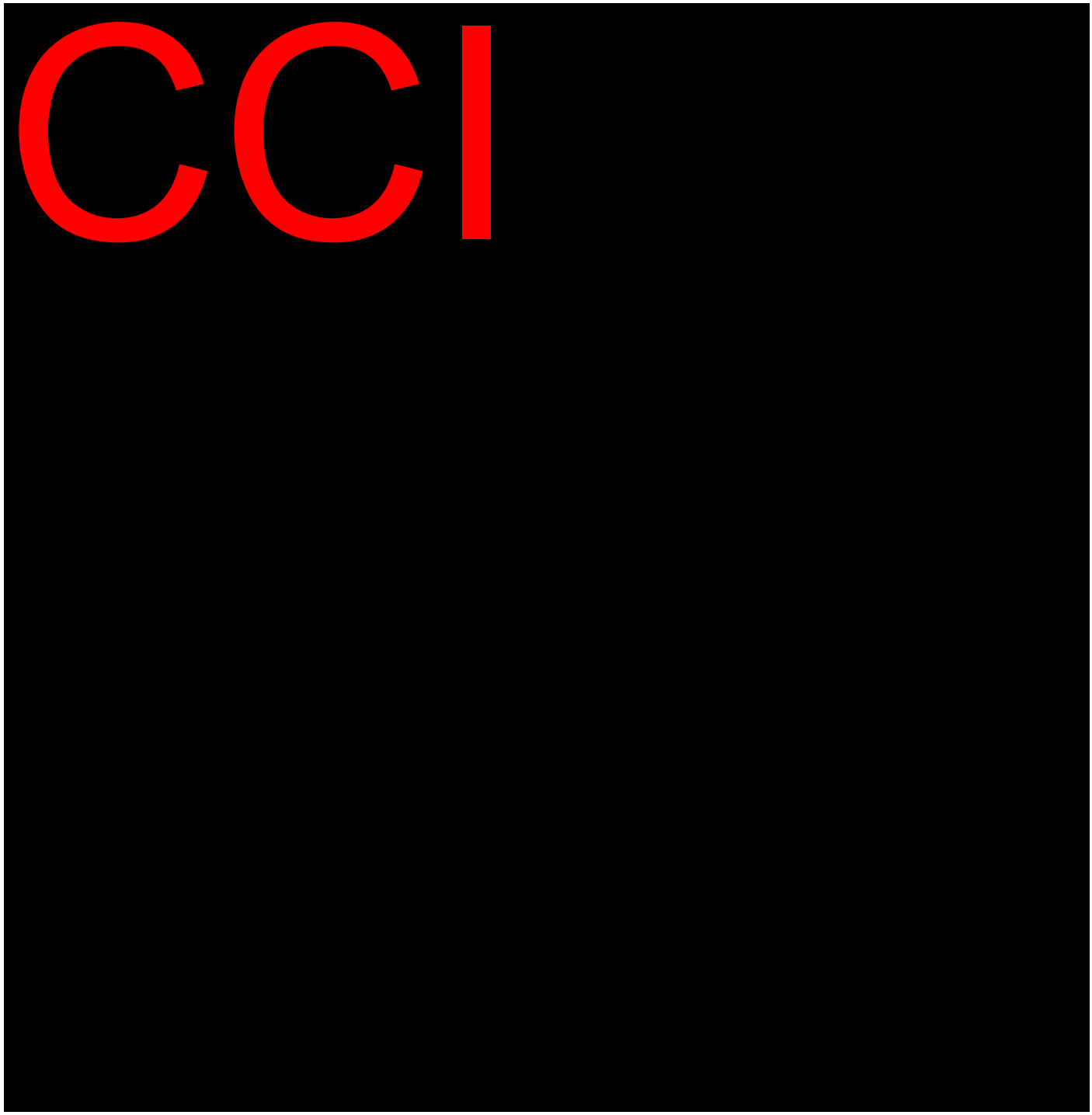
The primary analyses will be performed using a restricted maximum likelihood-based mixed models repeated measures (MMRM) technique with prespecified model terms (Section 9.4.1).

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report or SAP. Additional exploratory analyses of the data will be conducted as deemed appropriate.

9.4. Primary and Secondary Analyses

9.4.2. Key Secondary Analyses

CCI



~~Details of the specific testing methodology (including testing order, relationship and type I error allocation and propagation) will be specified in the SAP.~~ There will be no adjustments for multiplicity for analyses of other endpoints. If the multiple testing approach for key secondary measures only needs to be changed, the updated approach will be provided in the SAP, and it should not lead to modification of this protocol.

9.7. Other Analyses

9.7.3 Subgroup Analyses

Subgroup analyses will be performed for primary efficacy measure (change from baseline on number of migraine headache days) separately for each of the subgroup populations listed in Table CGAI.4. Subgroup analyses will be conducted only for the ITT patients in Study Period III.

Each of the subgroup analyses for the primary measure of change from baseline in the number of migraine headache days will be conducted using MMRM. The same MMRM model described in Section 9.4.1 will be used with terms of subgroup, subgroup-by-treatment, subgroup-by-month, and subgroup-by-treatment-by-month interactions added as additional covariates.

Table CGAI.~~3~~4. Definition of Subgroup Variables

11. References

Appendix 2 Schedule of Activities

Schedule of Activities, Protocol I5Q-MC-CGAI (Double-Blind Treatment Phase)

Study Period (SP)	SP I Screening	SP II Prospective Baseline	SP III Double-Blind Treatment				
(Target) Interval (days) since previous visit			30-45	14	16	30	30
Allowable range (days) between visits	3-45	30-40[a]					
Interval allowance (days)				+/- 1	+/- 3	+/- 2	+/- 2
Visit	1	2	3	4[b]	5	6	7
Month			0	0.5	1	2	3
Assessments and Procedures							
Physical examination[e]	X						
Neurological examination[c]	X						X

Schedule of Activities, Protocol I5Q-MC-CGAI (Open-Label and Post-Treatment Phases)

Study Period (SP)	**SP IV Open-Label**									**SP V Post-treatment**		
(Target) Interval (days) since previous visit	30	30	30	30	30	30	30	30	30	60	60	**ET**
Interval allowance (days)	+/- 2	+/- 2	+/- 2	+/- 2	+/- 2	+/- 2	+/- 2	+/- 2	+/- 2	+/- 5	+/- 5	
Visit	8	9	10	11	12	13	14	15	16	17	18	
Month	4	5	6	7	8	9	10	11	12	14	16	
Assessments and Procedures												
Neurological examination[c]			X			X			X		X	X
HDL			~~X~~[e]X[f]			~~X~~[e]X[f]			~~X~~[e]X[f]		~~X~~[e]X[f]	~~X~~[e]X[f]

[c] ~~Physical examinations at screening must include a neurological exam.~~ A neurological exam will be conducted at screening, Month 3 (final visit of double-blind treatment), Months 6, 9, and 12 (open-label treatment), and Month 16/early termination in order to assess for any signs of pre-existing or treatment-emergent neurological abnormalities such as stroke or other cerebrovascular events.

Leo Document ID = 486a5ad2-f054-4b02-bd31-b8ecc196a257

Approver: PPD
Approval Date & Time: 22-Jan-2016 17:08:37 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 22-Jan-2016 20:48:44 GMT
Signature meaning: Approved